New Directions in MDS Treatment: What's on the Horizon?

Tim Graubert, MD
Aplastic Anemia & MDS International Foundation
Patient and Family Conference
September 19, 2015

Types of Research Studies

<table>
<thead>
<tr>
<th>Preclinical</th>
<th>Clinical</th>
</tr>
</thead>
<tbody>
<tr>
<td>In vitro</td>
<td>Observational</td>
</tr>
<tr>
<td>In vivo</td>
<td>Interventional (purpose)</td>
</tr>
<tr>
<td></td>
<td>• Phase 1 (safe?)</td>
</tr>
<tr>
<td></td>
<td>• Phase 2 (effective?)</td>
</tr>
<tr>
<td></td>
<td>• Phase 3 (superior?)</td>
</tr>
<tr>
<td></td>
<td>• Phase 4 (safety)</td>
</tr>
</tbody>
</table>

MDS: Diagnosis/Classification

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

And:

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 Cytogenetics)


MDS: Diagnosis/Classification

Secondary AML:
- ≥20% myeloblasts in marrow or blood, 
or
- Abnormal karyotype typical for AML 
e.g., inv(16), t(8;21), t(15;17)

MDS: Diagnosis/Classification

Differential Diagnosis:
exclude other causes of cytopenias and dysplasia!

- 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.)
**MDS: Diagnosis/Classification**

**Essential testing:**

<table>
<thead>
<tr>
<th>Test</th>
<th>To evaluate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone marrow aspirate</td>
<td>Dysplasia, Blast count</td>
</tr>
<tr>
<td>Bone marrow biopsy</td>
<td>Cellularity, Iron content, Fibrosis</td>
</tr>
<tr>
<td>Cytogenetics (FISH)</td>
<td>Chromosomal lesions</td>
</tr>
<tr>
<td>B12, folate, Cu</td>
<td>Other causes</td>
</tr>
</tbody>
</table>

**Not currently standard of care:**

<table>
<thead>
<tr>
<th>Test</th>
<th>To evaluate</th>
</tr>
</thead>
<tbody>
<tr>
<td>SNP array</td>
<td>Copy number alterations</td>
</tr>
<tr>
<td>Flow cytometry</td>
<td>Aberrant antigen expression</td>
</tr>
<tr>
<td>Sequencing</td>
<td>Mutations</td>
</tr>
</tbody>
</table>

**What is a mutation?**

...TTGAGTCG....

...TTGAGTAG....

**Why should we care about gene mutations in MDS?**

1. **Biology**
   - Mutations give us clues about what went wrong with MDS cells.

2. **Diagnosis**
   - Mutations help us diagnose other bone marrow diseases.
   - (e.g., BCR/ABL = CML; JAK2V617F = Polycythemia vera)

3. **Prognosis**
   - Mutations help us predict outcome in other bone marrow diseases.
   - (e.g., DNMT3A in acute myeloid leukemia)

4. **Therapy**
   - Mutations help us choose the right drugs in other bone marrow diseases.
   - (e.g., BCR/ABL -> Imatinib)

**MDS: Diagnosis/Classification**

<table>
<thead>
<tr>
<th>WHO 2008</th>
<th>Common Name</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refractory cytopenia with unilineage dysplasia (RCUD)</td>
<td>RA</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>RN</td>
<td>&lt;1</td>
</tr>
<tr>
<td></td>
<td>RT</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Refractory anemia with ring sideroblasts</td>
<td>RARS</td>
<td>5</td>
</tr>
<tr>
<td>5q- syndrome</td>
<td>del(5q)</td>
<td>5</td>
</tr>
<tr>
<td>Refractory cytopenia with multilineage dysplasia</td>
<td>RCMRD</td>
<td>20</td>
</tr>
<tr>
<td>Refractory anemia with excess blasts, type 1</td>
<td>RAEB-1</td>
<td>20</td>
</tr>
<tr>
<td>Refractory anemia with excess blasts, type 2</td>
<td>RAEB-2</td>
<td>20</td>
</tr>
<tr>
<td>Unclassifiable</td>
<td>MDS-U</td>
<td>~10</td>
</tr>
<tr>
<td>Childhood MDS</td>
<td>RCC</td>
<td>Rare</td>
</tr>
</tbody>
</table>

**Proposed WHO 2016 Revisions:**

1. Eliminate “RA/RC” (e.g., RARS becomes MDS-RS)
   - Rationale: cytopenias captured in IPSS-R

2. MDS-RS definition broadened
   - Include multilineage dysplasia
   - Allow <15% RS if SF3B1 mutation present

3. MDS-del(5q) broadened
   - Allow one additional non-high risk cytogenetic lesion

4. Erythroid precursors no longer added to blast count
   - Avoids major clinical impact of diagnosing AEL vs. RAEB
### Risk Stratification: IPSS (1997)

<table>
<thead>
<tr>
<th>Prognostic Variable</th>
<th>Score Value</th>
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</thead>
<tbody>
<tr>
<td>Marrow Hts (%)</td>
<td>≤5, &gt;5-10, ≥11.0, 21-30</td>
</tr>
<tr>
<td>Cytopenias (*)</td>
<td>0, Good, Intermediate, Poor</td>
</tr>
</tbody>
</table>

#### Parameter Categories and Associated Scores

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Categories and Associated Scores</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytogenetics</td>
<td>Very good</td>
</tr>
<tr>
<td>Blasts</td>
<td>≤2%</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>≥10</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>≥0.8</td>
</tr>
<tr>
<td>Platelets</td>
<td>≥100</td>
</tr>
</tbody>
</table>


### In general, this is NOT rocket science*

- Better blood counts are good
- Not needing transfusions is good
- Lower blasts are good
- Having fewer genetic abnormalities is good
- Younger age is good
- Being able to function better is good

* Mikkael Sekeres, Cleveland Clinic

### MDS: Prognosis/Risk Stratification

* Caveats:
  - at diagnosis only
  - no disease-modifying therapy
  - de novo only


### Existing Therapies for MDS

**FDA-approved disease-modifying therapies:**
- Azacitidine
- Decitabine
- Lenalidomide

**Others:**
- Epo/G-CSF
- TPO agonists
- Iron chelation
- Immunosuppression (CSA/ATG)
- Stem cell transplantation

### General Treatment Paradigm for MDS

![General Treatment Paradigm for MDS](https://example.com/paradigm.png)

* Bejar and Steensma, Blood, 2014

### IPSS-R (2012)

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*IPSS-R: http://www.mds-foundation.org/ipss-r-calculator/*

(Also iOS, Android apps)
Low Risk MDS

- Lower Risk (VG,GJ)
- Isolated Anemia?
  - Yes: del(5q)?
    - Yes: Len
    - No: EPO=500?
  - No: HMA, IST, Clinical Trial

High Risk MDS

- Higher Risk (LP,VP)
- AlloSCT candidate?
  - Yes: AlloSCT
  - No: HMA, Clinical Trial

When to transplant?

- INT-2/H (converse for L/INT-1)
- Similar results for myeloablative SCT
- Definitive prospective trial ongoing
- <1,000 SCT per year for MDS in US


MDS Therapy: what’s on the horizon?

MDS Pipeline:

- >500 studies in ClinicalTrials.gov open and accruing
- Key observational trials:
  - Connect MDS/AML Disease Registry (NCT01688011)
  - NHLBI MDS Natural History Study (forthcoming)

MDS Therapy: what’s on the horizon?

- Key therapeutic trials:
  - Oral Aza and DAC (various)
  - Eltrombopag (various)
  - Checkpoint inhibitors (various)
  - CAR-T (NCT02003825)
  - IDH inhibitors (various)
  - Impact of Deferasirox on EFS (NCT00940602)
  - SMAD2/3 inhibitors (various)
  - Splicing modulators (forthcoming)
LUSPATERCEPT INCREASES HEMOGLOBIN AND REDUCES TRANSFUSION BURDEN IN PATIENTS WITH LOW OR INTERMEDIATE-1 RISK MYELODYSPLASTIC SYNDROMES (MDS): PRELIMINARY RESULTS FROM A PHASE 2 STUDY

Uwe Platbecker, MD
U Platbecker¹, U Giergling¹, A Giagounidis², K Goetze³, M Hankin⁴, JD Keating⁵, M Radsak⁶, J Wolff⁷, M Wiethöft⁸, K Goetz⁹, D Wilson⁹, A Laadem⁹, M Sherman⁹ and K Attie¹
¹Marien Hospital Düsseldorf; ²Technical University of Munich; ³Oncologische Schwerpunktstelle Darmstadt; ⁴University Medical Center Hamburg-Eppendorf; ⁵University of Michigan; ⁶Dana Farber Cancer Institute; ⁷University of Minnesota; ⁸Acceleron Pharma, Cambridge, MA; ⁹Celgene Corporation, Summit, NJ, USA

**A Phase 2, Dose-Finding Study of Sotatercept (ACE-011) in Patients With Lower-Risk Myelodysplastic Syndromes or Non-Proliferative Chronic Myelomonocytic Leukemia and Anemia Requiring Transfusion**


Department of Malignant Hematology, Moffitt Cancer Center, Tampa, FL, USA; Department of Leukemia and Hematopoietic Malignancies, The University of Texas MD Anderson Cancer Center, Houston, TX, USA; Department of Leukemia, Lazzaro Spallanzani National Institute of Haematology, Rome, Italy; Department of Leukemia, Fox Chase Cancer Center, Philadelphia, PA, USA; Department of Leukemia/Myelodysplastic Syndrome, The University of Texas MD Anderson Cancer Center, Houston, TX, USA; Department of Hematology and Medical Oncology, University Medicine of Goettingen, Germany; Department of Hematology and Medical Oncology, University of Minnesota, Minneapolis, MN, USA; Department of Leukemia, The University of Texas M.D. Anderson Cancer Center, Houston, TX, USA; Department of Leukemia, University of Texas MD Anderson Cancer Center, Houston, TX, USA; Department of Internal Medicine, University of Nebraska Medical Center, Omaha, NE, USA; Department of Medical Oncology, University of Texas MD Anderson Cancer Center, Houston, TX, USA; Department of Internal Medicine, University of Texas MD Anderson Cancer Center, Houston, TX, USA; Department of Hematology, University of Goettingen, Germany; Department of Medicine, University of Texas M.D. Anderson Cancer Center, Houston, TX, USA; Department of Hematology, University of Texas MD Anderson Cancer Center, Houston, TX, USA; Department of Medicine, University of Texas M.D. Anderson Cancer Center, Houston, TX, USA; Department of Medicine, University of Texas M.D. Anderson Cancer Center, Houston, TX, USA; Department of Internal Medicine, University of Nebraska Medical Center, Omaha, NE, USA; Department of Internal Medicine, University of Texas M.D. Anderson Cancer Center, Houston, TX, USA; Department of Medicine, University of Texas M.D. Anderson Cancer Center, Houston, TX, USA

**Sotatercept Preliminary Results**

**Luspatere PACE-MDS Study Overview**

- Phase 2, multicenter, open-label, dose-finding study in IPSS low/int-1 MDS
- Eligibility criteria:
  - nonresponsive/refractory to EPO or EPO > 500 UI/mL; no prior azacitidine or decitabine; no prior lenalidomide, ESA, G-CSF
- Primary efficacy endpoint:
  - Low transfusion burden (HTB, < 4U RBC/8 weeks): Hemoglobin increase of ≥ 1.5 g/dL for ≥ 2 weeks
  - High transfusion burden (HTB, ≥ 4U RBC/8 weeks):
    - Reduction of ≥24U or ≥50% units transfused over 8 weeks
- Luspatere administered SC every 3 weeks for 3 months in base study
- Patients may be eligible for additional 12 months treatment in extension study

NCT01749514
eudataCT 2012-002523-14

**Luspatere high dose group**

- **Transfusion Independence (TI)**
  - 10/28 (36%) patients achieved transfusion independence
- **Onset of TI**
  - 9 of the 10 TI patients had onset within the first 6 weeks of treatment
- **Duration of TI**
  - All 10 achieved transfusion independence for ≥10 weeks in this 3-month treatment study

**Transfusion Independence:** Transfusion-free for ≥8 weeks on treatment for patients who received at least one transfusion
Low Risk MDS

ELTROMBOPAG FOR LOW TO INT-2 RISK MDS
Danielle Townsley, MD, MSc
Hematology Branch
NHLBI, NIH

- 2nd generation small molecule thrombopoietin (TPO) receptor agonist
- Orally administered non-peptide
- FDA accelerated approval in 2008 for treatment of chronic ITP

ELTROMBOPAG

PHASE II, ELTROMBOPAG FOR MDS: NCT00961064
IPSS Low to Int-2 (NO RAEB/CMML)
AND
Significant cytopenia (Plts<20 or ANC<500 or Hb<9)*

- Eltrombopag 50 mg daily
- Dose escalation every 2 weeks to 150 mg daily
- BM biopsies performed serially
- Hematologic response at 16 weeks
- Enrolled n=21
- Planned n=30

RESPONSE TO ELTROMBOPAG
de novo, hypercellular MDS
73 yo female, IPSS Int-1: RCUD, normal cytogenetics, tx naive
Enrollment: Anemia/Thrombocytopenia

High Risk MDS

- Higher Risk (LP,VP)
- AlloSCT candidate?
- Yes
  - AlloSCT
- No
  - HMA, Clinical Trial
How do we improve the results with Aza?

**ALLG MDS**

The Addition of Lenalidomide to Azacitidine
Achieves Higher Responses But No Improvement In Twelve Month Clinical Benefit or PFS; main analysis of the Australian ALLG MDS4 Trial

Dr Melita Kenealy, on behalf of ALLG investigators (Melbourne, Australia)

13th International Symposium on Myelodysplastic Syndromes
Washington, DC
April 29 - May 2, 2015
Worse outcome with Len+Aza

![Graph showing worse outcome with Len+Aza](image)

**ALLG MDS4**

High Risk MDS

![Diagram showing high risk MDS](image)

**What happens when Aza stops working?**

- post aza n=435
- OS 5.6 months
- 2yr survival 15%

Fenaux Lancet Oncol 2009

Prebet JCO 2011

**IDH as a therapeutic target**

- IDH mutations occur in a spectrum of solid and hematologic tumors
  - IDH1m: ~3% of MDS
  - IDH2m: 3–6% of MDS


**IDH inhibitor trials**

- **14-035 (NCT02074839):**
  "Phase I multicenter study of AG-120 in patients with IDH1 mutant advanced hematologic malignancies"

- **13-371 (NCT01915498):**
  "Phase I multicenter study of AG-221 in patients with IDH2 mutant advanced hematologic malignancies"
**IDH2 inhibitor trial design**

Ongoing, first-in-human, dose escalation study:
- AG-221: First-in-class, oral, potent, reversible, selective inhibitor of mutated IDH2
- IDH2 mutation-positive hematologic malignancies, including relapsed or refractory AML, MDS, or untreated AML
- AG-221 in continuous oral dosing QD or BID daily, 28-day cycles

**Key outcome measures:**
- Safety and tolerability, DLTs
- MTD and recommended phase 2 dose

**IDH2i preliminary results**

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>CR</th>
<th>CRp</th>
<th>mCR</th>
<th>PR</th>
<th>SD</th>
<th>PD</th>
<th>Disease Not Evaluable</th>
<th>Total (n=45 evaluable)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤75</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>4</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>8/14 (57%)</td>
</tr>
<tr>
<td>100</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>4</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>11/14 (79%)</td>
</tr>
<tr>
<td>≥150</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>12/22 (55%)</td>
</tr>
</tbody>
</table>

**Total**: 25/45 (56%)

**Why should we care about gene mutations in MDS?**

1. **Biology**
   - Mutations give us clues about what went wrong with MDS cells.

2. **Diagnosis**
   - Mutations help us diagnose other bone marrow diseases.
     (e.g., BCR/ABL = CML; JAK2V617F = Polycythemia vera)

3. **Prognosis**
   - Mutations help us predict outcome in other bone marrow diseases.
     (e.g., DNMT3AR882H in acute myeloid leukemia)

4. **Therapy**
   - Mutations help us choose the right drugs in other bone marrow diseases.
     (e.g., BCR/ABL -> imatinib)

**Mutations affect prognosis**

- **Low Mut (+) vs. (-)**
- **Int-I Mut (+) vs. (-)**
- **Int-II Mut (+) vs. (-)**
- **High Mut (+) vs. (-)**

**Mutations in RNA splicing genes**


Splicing modulators on the horizon

- Cause splicing abnormalities
- Induce apoptosis in some cell lines in vitro and in vivo
- Bind SF3B complex (including SF3B1)

Lots of genes are mutated in MDS

- ~20 genes consistently mutated in >2% of MDS patients


Mutations without MDS

- ~10% of healthy people age >70

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>No. with Mutation</th>
<th>Total</th>
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<tbody>
<tr>
<td>20-30</td>
<td>0</td>
<td>240</td>
</tr>
<tr>
<td>30-40</td>
<td>3</td>
<td>855</td>
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<td>40-50</td>
<td>5</td>
<td>2894</td>
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<tr>
<td>50-60</td>
<td>13</td>
<td>5441</td>
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<td>60-70</td>
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<td>80-90</td>
<td>35</td>
<td>317</td>
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<td>90-100</td>
<td>7</td>
<td>86</td>
</tr>
<tr>
<td>100+</td>
<td>5</td>
<td>17</td>
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</tbody>
</table>


Clonal hematopoiesis of indeterminate potential ("CHIP")

- Elevated risk of MDS/AML
- But, not disease-defining for MDS!


Thanks!