MDS: Diagnosis/Classification

**Low Blood Counts:**
- 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
- S-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/B6 deficiency
- HIV or other viral infection
- Copper deficiency
- Alcohol abuse
- Medications (e.g. methotrexate, aspirin, 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>
**MDS: Diagnosis/Classification**

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>

---

**Genetics 101**

**What is a mutation?**

...TTGAGTCG....

...TTGAGTAG....

**Common MDS mutations**

---

**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 2016</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDS with single lineage dysplasia (MDS-SD)</td>
</tr>
<tr>
<td>MDS with multi-lineage dysplasia (MDS-MLD)</td>
</tr>
<tr>
<td>MDS with ring sideroblasts (MDS-RS)</td>
</tr>
<tr>
<td>MDS with isolated del(5q)</td>
</tr>
<tr>
<td>Refractory cytopenia with multilineage dysplasia (MDS-RCD)</td>
</tr>
<tr>
<td>MDS-EB1</td>
</tr>
<tr>
<td>MDS-EB2</td>
</tr>
<tr>
<td>MDS, Unclassifiable</td>
</tr>
<tr>
<td>Childhood MDS</td>
</tr>
</tbody>
</table>

**Risk Stratification: IPSS (1997)**

<table>
<thead>
<tr>
<th>Prognostic Variable</th>
<th>Score Value</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDS</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>MDS</td>
<td>5-8</td>
<td>1</td>
</tr>
<tr>
<td>MDS</td>
<td>1.5-19</td>
<td>1</td>
</tr>
<tr>
<td>MDS</td>
<td>20-29</td>
<td>1</td>
</tr>
<tr>
<td>MDS</td>
<td>30-65</td>
<td>1</td>
</tr>
<tr>
<td>MDS</td>
<td>&gt;65</td>
<td>1</td>
</tr>
</tbody>
</table>

- Marrow blast (%)<5: 50; >5: 30
- Karyotype (%): Good: 90; Intermediate: 60-90; Poor: ≤60
- Risk Category: Combined score
  - Low: ≤2
  - Int-1: 2.1-3.5
  - Int-2: 3.6-5.5
  - High: ≥5.6


**IPSS-R (2012)**

<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></td>
<td>Good</td>
</tr>
<tr>
<td></td>
<td>Intermediate</td>
</tr>
<tr>
<td></td>
<td>Poor</td>
</tr>
<tr>
<td></td>
<td>Very Poor</td>
</tr>
</tbody>
</table>

| Blasts           | 0                                |
|                 | 1-4                              |
|                 | 5-29                             |
|                 | >30                              |

| Hemoglobin      | >110                             |
|                 | 8-110                            |
|                 | ≤8                              |

| Neutrophils      | >6.5                             |
|                 | 2.5-6.5                          |
|                 | ≤2.5                            |

| Platelets        | ≥300                            |
|                 | 50-199                          |
|                 | 19-50                           |
|                 | ≤19                             |

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

(also iOS, Android apps)

| Platelets        | ≥300                            |
|                 | 50-199                          |
|                 | 19-50                           |
|                 | ≤19                             |


**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

* Mikael 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

```
MDS Diagnosis (WHO)
Symptomatic?
Yes → Observation
No → Risk Stratification (IPSS-R)
Risk Stratification (IPSS-R)
Yes → Observation
No → Progression
Lower Risk → Observation
Higher Risk → Observation
```

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 (NCT02775383)

Low Risk MDS

```
Lower Risk (WHO)
Isolated Anemia?
Yes → Observation
No → CAI?
Yes → Len
No → Observation
```

MDS Therapy: what’s on the horizon?

**MDS Pipeline:**
- **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 (NCT02841540)
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>

Low Risk MDS

- Phase 2, multicenter, open-label, dose-finding study in IPSS low/int-1 MDS
- Eligibility criteria: nonresponsive/refractory to ESA or EPO >500 U/L; no prior azacitidine or decitabine; no current lenalidomide, ESA, G-CSF
- Primary efficacy endpoint:
  - Low transfusion burden (ITR, <4U RBC/3 weeks; Hgb <10 g/dL)
  - Hemoglobin increase of ≥ 1.5 g/dL after ≥ 2 weeks
- High transfusion burden (HTR, >4U RBC/3 weeks)
- Randomized Phase III trial completed (Luspatercept vs. placebo)
- Study Overview
- Main findings (luspatercept)
  - 58 patients enrolled
  - At higher doses, 32/51 patients (63%) achieved improved blood counts
  - Minimal side effects (muscle aches), well-tolerated
  - Patients may be eligible for additional 12 months treatment in extension study

Luspatercept for the treatment of anaemia in patients with lower-risk myelodysplastic syndromes (PACE-MDS): a multicentre, open-label phase 2 dose-finding study with long-term extension study

Lancet Oncology, 2017; 18:1338-47
Main findings (luspatercept)

High Risk MDS

IDH as a therapeutic target

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, DLT
• MTD and recommended phase 2 dose

**IDH2i preliminary results**

<table>
<thead>
<tr>
<th>IDH2i</th>
<th>375 mg (n=6)</th>
<th>100 mg (n=14)</th>
<th>200 mg (n=22)</th>
<th>Total (n=45 evaluable)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>2</td>
<td>5</td>
<td>8</td>
<td>15</td>
</tr>
<tr>
<td>TTP</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>CRi</td>
<td>-</td>
<td>2</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>PR</td>
<td>-</td>
<td>3</td>
<td>7</td>
<td>10</td>
</tr>
<tr>
<td>CR</td>
<td>2</td>
<td>3</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>CRp</td>
<td>-</td>
<td>2</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>CR</td>
<td>1</td>
<td>1</td>
<td>-</td>
<td>2</td>
</tr>
</tbody>
</table>

**Benefit does not require CR**

*Clinical trial of oral spliceosome modulator currently enrolling (NCT02841540)*

**Splicing modulators on the horizon**

**Mutations affect prognosis**

- Low Risk
  - Mutation absent
- Low Risk
  - Mutation present
- Int-1 Risk

**Stem cell transplantation**

- No TP53, TET2, or DNMT3A
- TET2, or DNMT3A

**Mutations in RNA splicing genes**


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

Clonal hematopoiesis of indeterminate potential ("CHIP")

* elevated risk of MDS/AML
* but, Not disease-defining for MDS!

MDS Experts at Mass General

Leukemia Center
  Amir Fathi
  Phil Amrein
  Gaby Hobbs
  Eyal Attar
  Tim Graubert
  Hanno Hock
  Andy Brunner

BMT Center
  Yibin Chen
  Steve McAfee
  Tom Spitzer
  Paul O’Donnell
  Areej El-Jawahri
  Bimal Dey
  Zack DeFilipp

Thanks!

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