Myelodysplastic Syndromes: Disease Overview, Treatments, and New Therapies

Rafael Bejar MD, PhD

Aplastic Anemia & MDS International Foundation

Patient & Family Conference

March 30, 2019
Overview

• Introduction to MDS
• Clinical Practice
  - Making the diagnosis
  - Classification
  - Risk stratification
• Treatment Goals and Options
• Novel Therapies
• Questions and Answers
Myelodysplastic Syndromes

• Shared features:
  – Low blood counts
  – Clonal overgrowth of bone marrow 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

US SEER Cancer Registry Data

Incidence Rate per 100,000

Age

**Age and Sex in MDS**

- *Overall incidence in this analysis: 3.4 per 100,000*

<table>
<thead>
<tr>
<th>Age at MDS diagnosis (years)</th>
<th>Incidence rate (per 100,000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 40</td>
<td>0.1</td>
</tr>
<tr>
<td>40-49</td>
<td>0.7</td>
</tr>
<tr>
<td>50-59</td>
<td>2.0</td>
</tr>
<tr>
<td>60-69</td>
<td>7.5</td>
</tr>
<tr>
<td>70-79</td>
<td>20.9</td>
</tr>
<tr>
<td>≥ 80</td>
<td>36.4*</td>
</tr>
</tbody>
</table>

*P for trend < .05

Rollison DE et al Blood 2008;112:45-52.
**Etiology of MDS**

<10%

- Familial or Congenital
  - Often early onset and part of a larger syndrome

10-15%

- Topoisomerase II inhibitors
- Ionizing radiation
- DNA alkylating agents
  - Peaks 1-3 or 5-7 years following exposure

80%

- “De novo” (idiopathic, primary)
  - Median age ~71 years; increased risk with aging

Slide adapted from Dr. David Steensma
Making the Diagnosis
Diagnostic Overlap

Myelodysplastic Syndromes (MDS)

- Aplastic Anemia
- Paroxysmal Nocturnal Hematuria
- T-LGL
- Fanconi Anemia
- Acute Myeloid Leukemia (AML)
- Myeloproliferative Neoplasms
Low Blood Counts

71 year-old man with big red cells and low blood counts that developed over the past 6 months.

Normal Range

1.9  7.9  45
Cytopenia(s):
- Low hemoglobin, or
- Low neutrophil count, or
- Low platelet count

MDS “decisive” criteria:
- >10% dysplastic cells in 1 or more lineages, or
- 5-19% blasts, or
- Abnormal karyotype typical for MDS, or
- Specific mutation typical of MDS

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.)

Slide borrowed from Dr. David Steensma
Bone Marrow Biopsy

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From: NCCN Guidelines for Patients: MDS
The Bone Marrow
Chromosomes and Mutation Testing

human cell

chromosomes

DNA

gene

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Low Blood Counts

71 year-old man with big red cells and low blood counts that developed over the past 6 months.

Way too many cells in the bone marrow
4% blasts in aspirate
Dysplasia in all three cell types
Normal Karyotype (chromosomes ok)
Classification of MDS Subtypes
<table>
<thead>
<tr>
<th>Subtype</th>
<th>Blood</th>
<th>Bone marrow</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDS with single lineage dysplasia (MDS-SLD)(^3)</td>
<td>Single or bicytopenia</td>
<td>Dysplasia in ≥10% of one cell line, &lt;5% blasts</td>
</tr>
<tr>
<td>MDS with ring sideroblasts (MDS-RS)</td>
<td>Anemia, no blasts</td>
<td>≥15% of erythroid precursors w/ ring sideroblasts, or ≥5% ring sideroblasts if SF3B1 mutation present</td>
</tr>
<tr>
<td>MDS with multilineage dysplasia (MDS-MLD)</td>
<td>Cytopenia(s), &lt;1 x 10(^9)/L monocytes</td>
<td>Dysplasia in ≥10% of cells in ≥2 hematopoietic lineages, ± 15% ring sideroblasts, &lt;5% blasts</td>
</tr>
<tr>
<td>MDS with excess blasts-1 (MDS-EB-1)</td>
<td>Cytopenia(s), ≤2%–4% blasts, &lt;1 x 10(^9)/L monocytes</td>
<td>Unilineage or multilineage dysplasia, 5%–9% blasts, no Auer rods</td>
</tr>
<tr>
<td>MDS with excess blasts-2 (MDS-EB-2)</td>
<td>Cytopenia(s), 5%–19% blasts, &lt;1 x 10(^9)/L monocytes</td>
<td>Unilineage or multilineage dysplasia, 10%–19% blasts, ± Auer rods</td>
</tr>
<tr>
<td>MDS, unclassifiable (MDS-U)</td>
<td>Cytopenias, ±1% blasts on at least 2 occasions</td>
<td>Unilineage dysplasia or no dysplasia but characteristic MDS cytogenetics, &lt;5% blasts</td>
</tr>
<tr>
<td>MDS with isolated del(5q)</td>
<td>Anemia, platelets normal or increased</td>
<td>Unilineage erythroid dysplasia, isolated del(5q), &lt;5% blasts</td>
</tr>
<tr>
<td>Refractory cytopenia of childhood</td>
<td>Cytopenias, &lt;2% blasts</td>
<td>Dysplasia in 1–3 lineages, &lt;5% blasts</td>
</tr>
<tr>
<td>MDS with excess blasts in transformation (MDS-EB-T)(^2)</td>
<td>Cytopenias, 5%–19% blasts</td>
<td>Multilineage dysplasia, 20%–29% blasts, ± Auer rods</td>
</tr>
</tbody>
</table>
World Health Organization MDS categories (2016)

MDS Treatment is Highly Risk Stratified

Lower Risk
- Observation
- EPO
- Lenalidomide
- Immune suppression
- Iron Chelation

Higher Risk
- Azacitidine
- Decitabine
- Allo-HSCT
- Clinical Trials
### International Prognostic Scoring System

<table>
<thead>
<tr>
<th>Cytogenetic Risk Group</th>
<th>IPSS Karyotype Abnormalities (7 categories)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good</td>
<td>Normal, -Y, del(5q), del(20q)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>+8, any other single or double abnormality</td>
</tr>
<tr>
<td>Poor</td>
<td>Complex with ≥ 3 abnormalities, anomaly of chromosome 7</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>IPSS Parameter</th>
<th>Categories and Associated Scores</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytogenetic Risk Group</td>
<td>Good (0), Intermediate (0.5), Poor (1)</td>
</tr>
<tr>
<td>Bone Marrow Blast %</td>
<td>≤ 5% (0), 5%-10% (0.5), 11%-20% (1.5), 21%-30% (2)</td>
</tr>
<tr>
<td>Number of Cytopenias</td>
<td>0 or 1 (0), 2 or 3 (0.5)</td>
</tr>
</tbody>
</table>

#### Definition of Cytopenias
- Hemoglobin < 10 g/dL
- Neutrophil Count < 1.80 x 10^9/L
- Platelet Count < 100 x 10^9/L

<table>
<thead>
<tr>
<th>IPSS Risk Group</th>
<th>Points</th>
<th>% of Patients</th>
<th>Median survival, years</th>
<th>Time to 25% with AML, years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>0</td>
<td>33%</td>
<td>5.7</td>
<td>9.4</td>
</tr>
<tr>
<td>Intermediate-1</td>
<td>0.5 - 1</td>
<td>38%</td>
<td>3.5</td>
<td>3.3</td>
</tr>
<tr>
<td>Intermediate-2</td>
<td>1.5 - 2</td>
<td>22%</td>
<td>1.1</td>
<td>1.1</td>
</tr>
<tr>
<td>High</td>
<td>≥ 2.5</td>
<td>7%</td>
<td>0.4</td>
<td>0.2</td>
</tr>
</tbody>
</table>

International Prognostic Scoring System

LOWER Risk
- Low
- Int-1

HIGHER Risk
- Int-2
- High

Overall Survival, Years
- Patients, %
- Time to AML Evolution, Years
- Patients, %

Overall Survival:
- Low: n = 56
- Int-1: n = 314
- Int-2: n = 235
- High: n = 295

Time to AML Evolution:
- Low: n = 58
- Int-1: n = 267
- Int-2: n = 171
- High: n = 179
# IPSS-Revised (IPSS-R)

## Cytogenetic Risk Group

<table>
<thead>
<tr>
<th>IPSS-R Karyotype Abnormalities (19 categories)</th>
<th>Very good</th>
<th>Good</th>
<th>Intermediate</th>
<th>Poor</th>
<th>Very Poor</th>
</tr>
</thead>
<tbody>
<tr>
<td>del(11q), -Y</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Normal, del(20q), del(5q) alone or with 1 other anomaly, del(12p)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>+8, del(7q), i(17q), +19, +21, any single or double abnormality not listed, two or more independent clones</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>der(3q), -7, double with del(7q), complex with 3 abnormalities</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complex with &gt; 3 abnormalities</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

## IPSS-R Parameter

<table>
<thead>
<tr>
<th>IPSS-R Parameter</th>
<th>Categories and Associated Scores</th>
<th>Very good</th>
<th>Good</th>
<th>Intermediate</th>
<th>Poor</th>
<th>Very Poor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytogenetic Risk Group</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone Marrow Blast %</td>
<td>≤ 2%</td>
<td>&gt; 2% - &lt; 5%</td>
<td>5% - 10%</td>
<td>&gt; 10%</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>≥ 10</td>
<td>8 - &lt; 10</td>
<td>&lt; 8</td>
<td></td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Platelet Count (x 10^9/L)</td>
<td>≥ 100</td>
<td>50 - &lt; 100</td>
<td>&lt; 50</td>
<td></td>
<td>0</td>
<td>0.5</td>
</tr>
<tr>
<td>Absolute Neutrophil Count (x 10^9/L)</td>
<td>≥ 0.8</td>
<td>&lt; 0.8</td>
<td></td>
<td></td>
<td>0</td>
<td>0.5</td>
</tr>
</tbody>
</table>

## IPSS-R Risk Group

<table>
<thead>
<tr>
<th>IPSS-R Risk Group</th>
<th>Points</th>
<th>% of Patients</th>
<th>Median survival, years</th>
<th>Time to 25% with AML, years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very low</td>
<td>≤ 1.5</td>
<td>19%</td>
<td>8.8</td>
<td>Not reached</td>
</tr>
<tr>
<td>Low</td>
<td>&gt; 1.5 - 3</td>
<td>38%</td>
<td>5.3</td>
<td>10.8</td>
</tr>
<tr>
<td>Intermediate</td>
<td>&gt; 3 - &lt; 4.5</td>
<td>20%</td>
<td>3</td>
<td>10.8</td>
</tr>
<tr>
<td>High</td>
<td>&gt; 4.5 - 6</td>
<td>13%</td>
<td>1.6</td>
<td>1.4</td>
</tr>
<tr>
<td>Very High</td>
<td>&gt; 6</td>
<td>10%</td>
<td>0.8</td>
<td>0.73</td>
</tr>
</tbody>
</table>

## Limitations of the IPSS-R

<table>
<thead>
<tr>
<th>Risk group</th>
<th>Included karyotypes (19 categories)</th>
<th>Median survival, months</th>
<th>Proportion of patients in this group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very good</td>
<td>del(11q), -Y</td>
<td>60.8</td>
<td>2.9%</td>
</tr>
<tr>
<td>Good</td>
<td>Normal, del(20q), del(5q) alone or with 1 other anomaly, del(12p)</td>
<td>48.6</td>
<td>65.7%</td>
</tr>
<tr>
<td>Intermediate</td>
<td>+8, del(7q), i(17q), +19, +21, any single or double abnormality not listed, two or more independent clones</td>
<td>26.1</td>
<td>19.2%</td>
</tr>
<tr>
<td>Poor</td>
<td>der(3q), -7, double with del(7q), complex with 3 abnormalities</td>
<td>15.8</td>
<td>5.4%</td>
</tr>
<tr>
<td>Very poor</td>
<td>Complex with &gt; 3 abnormalities</td>
<td>5.9</td>
<td>6.8%</td>
</tr>
</tbody>
</table>

### Cytogenetic risk group

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Categories and Associated Scores</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytogenetic risk group</td>
<td>Very good</td>
</tr>
<tr>
<td>0%</td>
<td>1%</td>
</tr>
<tr>
<td>Marrow blast proportion</td>
<td>&lt; 2%</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>0%</td>
</tr>
<tr>
<td>Platelet count (x 10^9/L)</td>
<td>&gt; 100%</td>
</tr>
<tr>
<td>Abs. neutrophil count (x 10^9/L)</td>
<td>≥ 0.8%</td>
</tr>
</tbody>
</table>

### Considerations

- **Considers only UNTREATED patients**
- **IPSS-R does not consider somatic mutations**
- **Somatic mutations are common in MDS**
- **Several mutated genes have prognostic significance independent of the IPSS-R**

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### Survival Curves

- **Very low**
- **Low**
- **Intermediate**
- **High**
- **Very high**

---

### Median Survival

- **Very low**: 8.8 years
- **Low**: 5.3 years
- **Intermediate**: 3.0 years
- **High**: 1.6 years
- **Very High**: 0.8 years
Most Frequently Mutated Genes

Tyrosine Kinase Pathway
- JAK2
- KRAS
- BRAF
- FLT3
- NRAS
- CBL
- PTPN11

Transcription Factors
- RUNX1
- ETV6
- GATA2
- WT1
- PHF6

Others
- TP53
- STAG2
- SMC3
- RAD21
- DDX41
- BCOR/L1
- NPM1

Epigenetic Dysregulation
- IDH 1 & 2
- DNMT3A
- EZH2
- TET2
- ASXL1
- UTX
- ATRX
- SETBP1

Splicing Factors
- SF3B1
- U2AF1
- ZRSR2
- SF1
- SRSF2
- U2AF2
- PRPF40B
- PRPF8
- SF3A1
30% of MDS patients have a mutation in one of these genes
These mutations indicate more severe disease!

Bejar et al. NEJM. 2011;364:2496-506.
Bejar et al. JCO. 2012;30:3376-82.
Impact of Mutations by IPSS Group

Bejar et al. NEJM. 2011;364:2496-506.
Impact of Mutations by IPSS-R Group

- **TP53**
- **ETV6**
- **ASXL1**
- **EZH2**
- **RUNX1**

![Graphs showing survival rates by IPSS-R Group](image-url)
Prognostic Mutations by Blast % (<5%)
Prognostic Mutations by Blast % (5-30%)

34%
Risk Adapted
Patient Specific 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** – often the best option
Risk-Adapted Therapy

Lower Risk
- Observation
- EPO
- Lenalidomide
- Immune suppression
- Iron Chelation

Higher Risk
- Azacitidine
- Decitabine
- Allo-HSCT
- Clinical Trials
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.
Guidelines for Lower Risk MDS

Primary Goal: to improve QUALITY OF LIFE

IPSS: Low/Intermediate-1
WPSS: Very Low, Low, Intermediate

Clinically significant cytopenia(s) → Supportive care as an adjunct to treatment

Symptomatic anemia
- del(5q) ± other cytogenetic abnormalities
- No del(5q) ± other cytogenetic abnormalities

Clinically relevant thrombocytopenia or neutropenia
Treating Lower Risk MDS

Primary Goal: to improve QUALITY OF LIFE

What if treatment is needed?

1. 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!
Treating Lower Risk MDS

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

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

**ESAs** – act like our own erythropoietin

<table>
<thead>
<tr>
<th>Serum EPO level (U/L)</th>
<th>RBC transfusion requirement</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;100</td>
<td>&lt;2 Units/month = +2 pts</td>
</tr>
<tr>
<td>100-500</td>
<td>≥2 Units/month = -2 pts</td>
</tr>
<tr>
<td>&gt;500</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Total Score</th>
<th>Response Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>High likelihood of response: &gt; +1</td>
<td>74% (n=34)</td>
</tr>
<tr>
<td>Intermediate likelihood: -1 to +1</td>
<td>23% (n=31)</td>
</tr>
<tr>
<td>Low likelihood of response: &lt; -1</td>
<td>7% (n=39)</td>
</tr>
</tbody>
</table>

Hellstrom-Lindberg E et al *Br J Haem* 2003; 120:1037
Primary Goal: to improve QUALITY OF LIFE

Is a combination of LEN +/- ESA likely to work?

In non-del(5q) MDS patients:

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)
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

Iron Balance and Transfusions

Daily intake
1.5 mg (0.04%)
Tightly regulated

3-4 grams of Iron in the body

Daily losses only
1.5 mg (0.04%)
Not regulated!

Every three units of blood
What About Iron Chelation?

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.

TELESTO
Deferasirox in LR/Int-1 MDS With Transfusional Iron Overload

Multicenter, randomized (2:1), double-blind, placebo-controlled, phase 2 trial
Low- or Int-1-risk MDS per IPSS, serum ferritin > 1000 μg/L and < 2500 μg/L (planned N = 630)

Deferasirox
10 mg/kg/d (d 1-14)
20 mg/kg/d (wk 2-12)
Up to 40 mg/kg/d (> 12 wk)
(n = 420)

Placebo
10 mg/kg/d (d 1-14)
20 mg/kg/d (wk 2-12)
Up to 40 mg/kg/d (> 12 wk)
(n = 210)

Continue treatment ≤ 5 y; interim analysis at 50% of primary composite events (~3 y) and 75% of primary composite events (~4 y)

• Primary endpoint: EFS (includes death and nonfatal cardiac and liver function events)
• Secondary endpoints: hematologic improvement, OS, disease progression, endocrine and metabolic function, safety, serum ferritin > 2 × BL

Figure 1. Kaplan-Meier curve of event-free survival
Randomized treatment
Deferasirox — Placebo + Censored

Figure 2. Serum ferritin levels over time by treatment group
How to Chelate Iron

Three ways are FDA approved:

- Deferoxamine (Desferal) – subcutaneous pump 8-12 hrs/day
- Deferasirox (Exjade/Jadenu) – powder/pill – 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) or after ESA

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!**
Novel Treatments for Lower Risk MDS
Luspatercept

ESAs
TPO mimetics
G-CSF (neupogen)

EPO/ESAs
Hemoglobin synthesis

BFU-E  CFU-E  Pro E  Baso E  Poly E  Ortho E  Retic  RBC

TGF-β
Luspatercept

ESAs
TPO mimetics
G-CSF (neupogen)

EPO/ESAs
Hemoglobin synthesis

BFU-E  CFU-E  Pro E  Baso E  Poly E  Ortho E  Retic  RBC

TGF-β
Promoting Red Cell Production

Luspatercept (ACE-536) and Sotatercept (ACE-011)
Promoting Red Cell Production

Luspatercept (ACE-536) and Sotatercept (ACE-011)
Increase in Mean Hemoglobin in LTB Patients with > 3 Months of Treatment (Extension Study)

- 11/13 (85%) HI-E responders; median time to response: 6 weeks

LTB: Low transfusion burden patients (< 4 Units/8 wk, Hb <10 g/dL)

Data as of 04 Mar 2016
**MEDALIST Trial - Change in Hemoglobin Concentration**

- **LS mean difference (95% CI) for luspatercept responders versus placebo:** 1.08 (0.84, 1.31), *P* < 0.0001.

Only patients with RBC-TI ≥ 8 weeks during weeks 1–24 are included. Hb measurement was excluded within 14 days after a RBC transfusion unless within 3 days prior to another RBC transfusion. Mean and SE were not calculated if the number of patients was < 8 in the luspatercept non-responder group or < 4 in the placebo group. SE, standard error.

**Number of patients**

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Responder</th>
<th>Non-responder</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>153</td>
<td>24 36 55</td>
<td>53 52 50 42</td>
<td>76 32</td>
</tr>
<tr>
<td>24</td>
<td>33 51 61</td>
<td>60 53 34 45</td>
<td>36 41</td>
</tr>
<tr>
<td>53</td>
<td>60 53 42</td>
<td>76 32 44 47</td>
<td>41 44</td>
</tr>
<tr>
<td>52</td>
<td>34 45 56</td>
<td>52 29 44 47</td>
<td>44 35</td>
</tr>
<tr>
<td>50</td>
<td>56 48 45</td>
<td>44 35 32 45</td>
<td>32 45</td>
</tr>
</tbody>
</table>

- Median peak hemoglobin increase in luspatercept responders: 2.55 g/dL (1–4.1 g/dL)

- **Hb Mean Change (± SE) From Baseline (g/dL)**

  - **Analysis Week Visit**
  - **Responser receiving luspatercept**
  - **Non-responder receiving luspatercept**
  - **Placebo**

  

  ![Graph showing Hb Mean Change (± SE) From Baseline (g/dL)](image)

  - **Analysis Week Visit**
  - **P < 0.0001**

  - **Baseline**
  - **1 2 3 6 9 12 13 15 18 21 24**

  - **Hb Mean Change (± SE) From Baseline (g/dL)**

  - **Responder receiving luspatercept**
  - **Non-responder receiving luspatercept**
  - **Placebo**
**Platelet Growth Factors**

**Eltrombopag or Romiplostim** - TPO mimetics

Eltrombopag and Romiplostim - approved, but not yet in MDS

Initial concern about increasing blasts and risk of AML

Follow-up suggests both drugs are safe in lower risk patients

Mittleman M et al *ASH Abstracts*, 2013. Abstract #3822  
Randomized study of **Azacitidine 75 mg/m^2 x 3 days** vs. **Decitabine 20 mg/m^2 x 3 days** on a 28-day cycle in lower-risk MDS.

**Conclusion – 3-day Decitabine is a viable regimen for LR MDS**

<table>
<thead>
<tr>
<th>Table 2. Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parameter</td>
</tr>
<tr>
<td>Morphologic response, N</td>
</tr>
<tr>
<td>CR</td>
</tr>
<tr>
<td>mCR</td>
</tr>
<tr>
<td>HI</td>
</tr>
<tr>
<td>Overall</td>
</tr>
<tr>
<td>Transfusion response, N</td>
</tr>
<tr>
<td>RBC</td>
</tr>
<tr>
<td>Platelets</td>
</tr>
<tr>
<td>RBC + Platelets</td>
</tr>
<tr>
<td>Overall</td>
</tr>
</tbody>
</table>

Treatment of Higher Risk MDS
Inhibitors of DNA methyl transferases:

Azacitidine
VIDAZA

Decitabine
DACOGEN

5-azacytidine (azacitidine)

5-aza-2'-deoxycytidine (decitabine)

Hypomethylating Agents

Graph showing survival rates:
- Azacitidine
- Conventional care

Number at risk:
- Azacitidine: 179
- Conventional care: 179

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>Azacitidine</th>
<th>Conventional care</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>152</td>
<td>132</td>
</tr>
<tr>
<td>5</td>
<td>130</td>
<td>95</td>
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<td>10</td>
<td>85</td>
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<td>15</td>
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<td>20</td>
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<td>25</td>
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<td>5</td>
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<tr>
<td>30</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>35</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*Analysed Population = All Patients*

Percent Alive Without AML:
- Decitabine (N=89)
- Supportive Care (N=81)
AZA-001 Phase III: AZA vs. Id-ARA-C vs. supportive care

OS benefit: + 9.5 mos

Time to AML: 17.8 vs. 11.5 mos

TI: 45% vs. 11%

Azacitidine Response:

ORR: ~50%

CR: ~17%

Median time to response: 3 cycles (81% by cycle 6)

Log-rank $P=0.0001$

HR=0.58 (95% CI: 0.43-0.77)

AZA-001: Time to First Response (CR, PR, HI)

- 90%, 9 cycles
- 81%, 6 cycles
- 50%, 3 cycles

Range: 1-22 cycles

Number of Subjects (N = 179)

91 34 12 6 3 1 1 1

Stem Cell Transplantation
The Allogeneic Transplant Process

1. Collection: Stem cells are collected from the patient's bone marrow or blood.
2. Processing: Bone marrow or peripheral blood is taken to the processing laboratory where the stem cells are concentrated and prepared for the freezing process.
3. Cryopreservation: Bone marrow or blood is preserved by freezing (cryopreservation) to keep stem cells alive until they are infused into the patient's bloodstream.
4. Chemotherapy: High dose chemotherapy and/or radiation therapy is given to the patient.
5. Infusion: Thawed stem cells are infused into the patient.
Trends in Transplantation

Goal of Hematopoietic Stem Cell Transplantation:

#1) Replace a dysfunction host hematopoietic system with normal, healthy donor marrow.

#2) Allow the donor immune system to destroy the abnormal, diseased host cells (MDS).

Conditioning  Engraftment  Graft-vs.-MDS
<5% of patients with MDS currently undergo allogeneic SCT

“Only curative therapy”

Patients who go in to RIC allo SCT with <10% blasts appear to have lower relapse

Optimal timing, pre-transplant therapy, conditioning unclear; usually reserved for IPSS Int-2/High (IBMTR Markov analysis)

Transplant candidate
Donor identified

Survives transplant; MDS cured! (35-40%)

Survives transplant; MDS recurs/persists (30-40%)

Dies from complication of transplant (20-25%)

Obstacles to Transplantation

Graft Rejection
  – need to suppress the host immune system

Toxicity
  – infection
  – organ damage
  – graft versus host disease

Finding a Donor
  – siblings match only 25% of the time
  – and are often too old or ill to donate
Overcoming Obstacles

Avoiding Graft Rejection
  – better approaches to immune suppression

Less Toxicity
  – better supportive care
  – better antigen matching
  – reduced intensity conditioning

Alternative Sources for Stem Cells
  – haploidentical – “half” match
  – umbilical cord blood stem cells
Reduce intensity conditioning transplantation in Older Patients with *De Novo* MDS

---

**IPSS Low/Int1**

- **Nontransplantation therapy**
- **RIC transplantation**

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>Overall Survival (probability)</th>
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<tbody>
<tr>
<td>0</td>
<td>1.0</td>
</tr>
<tr>
<td>20</td>
<td>0.8</td>
</tr>
<tr>
<td>40</td>
<td>0.6</td>
</tr>
<tr>
<td>60</td>
<td>0.4</td>
</tr>
<tr>
<td>80</td>
<td>0.2</td>
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<tr>
<td>100</td>
<td>0.2</td>
</tr>
<tr>
<td>120</td>
<td>0.1</td>
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<tr>
<td>140</td>
<td>0.1</td>
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</tbody>
</table>

*P < .001*

**IPSS Int2/High**

- **Nontransplantation therapy**
- **RIC transplantation**

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<th>Time (months)</th>
<th>Overall Survival (probability)</th>
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<td>120</td>
<td>0.1</td>
</tr>
<tr>
<td>140</td>
<td>0.1</td>
</tr>
</tbody>
</table>

*P < .001*

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Trends in Allogeneic Transplants by Transplant Type and Recipient Age* 1990-2010

* Transplants for AML, ALL, NHL, Hodgkin Disease, Multiple Myeloma
Allogeneic Transplants for Age > 20yrs, Registered with the CIBMTR, 1993-2010
- by Donor Type and Graft Source -

Number of Transplants

<table>
<thead>
<tr>
<th>Year</th>
<th>Related BM/PB</th>
<th>Unrelated BM</th>
<th>Unrelated PB</th>
<th>Unrelated CB</th>
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<tbody>
<tr>
<td>1993-94</td>
<td>7,000</td>
<td>1,000</td>
<td>1,000</td>
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<tr>
<td>1995-96</td>
<td>9,000</td>
<td>1,000</td>
<td>1,000</td>
<td>1,000</td>
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<tr>
<td>1997-98</td>
<td>11,000</td>
<td>1,000</td>
<td>1,000</td>
<td>1,000</td>
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<tr>
<td>1999-00</td>
<td>12,000</td>
<td>1,000</td>
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<td>2001-02</td>
<td>13,000</td>
<td>1,000</td>
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<tr>
<td>2003-04</td>
<td>14,000</td>
<td>1,000</td>
<td>1,000</td>
<td>1,000</td>
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<tr>
<td>2005-06</td>
<td>15,000</td>
<td>1,000</td>
<td>1,000</td>
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<tr>
<td>2007-08</td>
<td>16,000</td>
<td>1,000</td>
<td>1,000</td>
<td>1,000</td>
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<tr>
<td>2009-10</td>
<td>17,000</td>
<td>1,000</td>
<td>1,000</td>
<td>1,000</td>
</tr>
</tbody>
</table>
*TP53* mutated MDS

*Poor prognosis due to early relapse*

- **TP53 mutation**
  - Median OS = 8 months
- **No TP53 mutation**
Novel Treatments for Higher Risk MDS
Guidelines for Higher Risk MDS

Goal: to improve **DURATION OF LIFE**

Special Considerations:

**Refer for Transplant Early**
- Even patients in their 70’s can benefit from RIC transplant

**AZA > DEC (for now)**
- AZA has been shown to have a survival advantage, DEC has not (yet)

**Don’t forget Quality of Life**
- Consider treatment palliative and weigh against patient needs

**Look for Clinical Trials**
- Few option after AZA are available and none are approved
Outcomes After Azacitidine

- Data available on 435 pts
  - from AZA001, J9950, J0443, French compassionate program
- Overall median survival after azacitidine failure: 5.6 months

<table>
<thead>
<tr>
<th>Subsequent therapy</th>
<th>Number of patients (%)</th>
<th>Median survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allogeneic transplant</td>
<td>37 (9%)</td>
<td>19.5 months</td>
</tr>
<tr>
<td>Investigational therapy</td>
<td>44 (10%)</td>
<td>13.2 months</td>
</tr>
<tr>
<td>(e.g. IMiD, HDACi, other)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intensive cytotoxic therapy</td>
<td>35 (8%)</td>
<td>8.9 months</td>
</tr>
<tr>
<td>(e.g., 3&amp;7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low-dose chemotherapy</td>
<td>32 (7%)</td>
<td>7.3 months</td>
</tr>
<tr>
<td>(e.g. LDAC, 6-MP)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Palliative / supportive care</td>
<td>122 (28%)</td>
<td>4.1 months</td>
</tr>
<tr>
<td>Subsequent therapy unknown</td>
<td>165 (38%)</td>
<td>3.6 months</td>
</tr>
</tbody>
</table>
Treatment of Higher Risk MDS

We need **BETTER** therapies!

We need **MORE** therapies!
### Rigosertib Phase III Result

<table>
<thead>
<tr>
<th></th>
<th>Rigosertib</th>
<th>BSC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number (%) of deaths</strong></td>
<td>161 (81%)</td>
<td>81 (81%)</td>
</tr>
<tr>
<td><strong>Median follow-up (months)</strong></td>
<td>17.6</td>
<td>19.5</td>
</tr>
<tr>
<td><strong>Median survival (months)</strong></td>
<td>8.2</td>
<td>5.9</td>
</tr>
<tr>
<td><strong>95% CI</strong></td>
<td>6.0 - 10.1</td>
<td>4.1 - 9.3</td>
</tr>
<tr>
<td><strong>Stratified HR (rigosertib/BSC)</strong></td>
<td>0.87</td>
<td></td>
</tr>
<tr>
<td><strong>95% CI</strong></td>
<td>0.67 - 1.14</td>
<td></td>
</tr>
<tr>
<td><strong>Stratified log-rank p-value</strong></td>
<td>&lt;0.0001</td>
<td>0.33</td>
</tr>
</tbody>
</table>

- **All Patients**

![Survival Curve](image)
Per Prebet 2011, “Primary HMA Failure” was defined as either no response to or progression during HMA therapy.

ONTIME Trial: Median Overall Survival for Pts with Primary HMA Failure - Blinded, Centralized Assessment

At risk
- RIG 117, 93, 70, 54, 38, 21, 9, 6, 3, 2, 1
- BSC 52, 33, 22, 15, 8, 6, 3, 1, 1, 1

Medians:
- RIG 8.6 mo
- BSC 4.5 mo

Stratified log-rank P = 0.011
HR = 0.63 (95% CI: 0.44-0.90)
### SGI-110 Phase II Results

<table>
<thead>
<tr>
<th></th>
<th>60 mg/m2 (n=53)</th>
<th>90 mg/m2 (n=49)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>8-week RBCs Transfusion Independent n (%)</strong></td>
<td>7/27 (26%)</td>
<td>5/24 (21%)</td>
</tr>
<tr>
<td><strong>8-week Platelet Transfusion Independent n (%)</strong></td>
<td>4/13 (31%)</td>
<td>5/15 (33%)</td>
</tr>
</tbody>
</table>
In Phase III study in combination with Azacitididine for higher risk MDS/CMML/AML
Venetoclax - a BCL2 specific inhibitor

A restoration of apoptosis through BCL2 inhibition

Approved for CLL and for AML in combination with an HMA
In trials for MDS in combination with HMA
Immune Regulation

PD1 and PD-L1 Inhibitors

Currently in clinical trials around the country (Stanford)
Immunologic Therapy

Killer T-cell

Tumor Cell

Plasma B-cell

Chimeric Antigen Receptor

Monoclonal antibody

Immune receptor

CD3ζ

FceRIγ

scFv
Hinge
TM
Signaling chain
Immunologic Therapy

Chimeric Antigen Receptor
Modified T-cell

Tumor Cell
From Genetic Biomarkers to Disease Targets

Skin Biopsy

Bone Marrow Aspirate

Blood Apheresis

Whole Exome and Whole Transcriptome Sequencing CD34+ and monocytes

Isolation of Autologous Killer T-Cells and Antigen Presenting B-Cells

Somatic Mutations Expressed by MDS Cells
Genetically Targeted Immunotherapy

Isolation of Autologous Killer T-Cells

Incubation of Antigen Presenting Cells And Killer T-Cells

Ex-vivo Selection and Expansion of Antigen Reactive T-Cells

Somatic Mutations Expressed by MDS Cells

Antigen Presenting Cells + Synthetic HLA-Compatible Mutated Peptide

Patient Infusion!
Acknowledgements

MDS Center of Excellence at UC San Diego

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Dan Kauffman
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- Hematopathology
- BMT Group
- Hematology Group

Bejar Lab

Tim Luger
Tiffany Tanaka
Armon Azizi

Soo Park
Brian Reilly
Raluca Ciochina

All of our PATIENTS and INFUSION CENTER nurses and staff!

UC San Diego
Moore Cancer Center

AA-MDS
International Foundation