MDS – Therapies and Treatment Options 2019

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Assistant Professor, Temple University School of Medicine.
Objectives

• Understand the difference between low-risk and high risk MDS
• Understand the MDS classification and scoring systems and what they mean in regards to your diagnosis
• Understand your treatment options as well as the advances in MDS treatment, particularly bone marrow transplants in older MDS patients
• Understand what personalized medicine means in relationship to MDS
• Understand how to take an active role in your care
I have anemia?

72 year-old woman with worsening shortness of breath, now has blood test which showed

- WBC: 5,000
- Hgb: 7
- Platelets: 250,000

Hemoglobin was 11 6 months ago.
Questions

• What do I have?

• Can I take iron or other supplements to help?
I have anemia?

- Vitamin B12 deficiency
- Copper deficiency
- Alcohol abuse
- Anemia of CKD
- Iron deficiency
- Anemia of chronic disease
- MDS
- Thyroid disorder
MDS – Let’s build a definition

• Myelo – Bone marrow
MDS – What does bone marrow do?

Blood Cells

- Stem Cell
- Red Blood Cells
- White Blood Cells
- Platelets
Differentiation

Transformation

Stem cell

Blasts

Normal

Red

Platelets

White

10,000,000,000 WBCs/day

200,000,000,000 RBCs/day

100,000,000,000 Platelets/day

Modified from slide from Dr. Rafel Bejar
MDS – Let’s build a definition

- **Dysplastic** – Funny looking

- Abnormal appearance of cells when viewed under the microscope

- Difference in shapes, sizes, granules (particles with the cell)

- Can be caused by many conditions, not only MDS
Differentiation

Transformation

Normal vs Dysplastic cells

Norman vs Dysplastic cells

Slide borrowed from Dr. Rafel Bejar
MDS – Let’s build a definition

• Syndrome – Collection of symptoms
MDS Incidence Rates 2000-2008

US SEER Cancer Registry Data

Incidence Rate per 100,000

Etiology of MDS

- **85%**
  - "De novo"
  - (idiopathic, primary)

- **10-15%**
  - Ionizing radiation,
  - Chemo (DNA alkylating agents)
  - (chlorambucil, melphalan, cyclophosphamide, etc.)

- **<5%**
  - Chemotherapy
  - (Topoisomerase II inhibitors)
  - (etoposide, anthracyclines, used in Rx of Breast Ca etc.)

Median age ~71 years; increased risk with **aging**

Between 5-10 **years following exposure**

Peaks **1-3 years following exposure**

Slide borrowed from Dr. David Steensma
Risk factors for MDS

Environmental

AGING
Exposure to DNA alkylating agents (*chlorambucil, melphalan, cyclophosphamide*)
Exposure to topoisomerase II inhibitors (*etoposide, anthracyclines*)
Exposure to ionizing radiation
Environmental / occupational exposures (*hydrocarbons etc.*)

Antecedent acquired hematological disorders
Aplastic anemia (15-20%)
PNH (5-25%)

Inborn

Fanconi anemia
Familial Platelet Disorder with AML Predisposition ("FPD-AML") (*RUNX1, GATA2* mutant
(*MonoMACsyndrome*: monocytopenia, B/NK lymphopenia, atypical mycobacteria and viral and other infections, pulmonary proteinosis, neoplasms)

Other congenital marrow failure syndromes or DNA repair defects (*Bloom syndrome, ataxia-telangiectasia, etc.*)
Familial syndromes of unknown origin

Slide borrowed from Dr. David Steensma
Genetics - Basics

Adapted from National Human Genome Research Institute
Mutation refers to permanent change in genetic material.
Mutations accumulate and Get fixed
When We are Young
Mutations accumulate and get fixed
(Less well as we age)
Mutations may occur in CRITICAL areas of our genes.
Age related Clonal hematopoiesis

Jaiswal et al NEJM
Clonal hematopoiesis is associated with increased risk of hematologic malignancy

HR 11, 95% CI 3.9 to 33, p<0.001, adjusted for age, sex and T2D status
Differentiation

Transformation

Normal

Early MDS

Advanced MDS

Secondary AML

Slide borrowed from Dr. Rafel Bejar
Ineffective Blood cell production leads to low blood counts

Clonal expansion of abnormal cells

Paradox of low counts in a hypercellular bone marrow

Risk of transformation to Acute Myeloid leukemia
  • (Pre-leukemia?)
Signs and Symptoms

Anemia
- Fatigue
- Shortness of breath
- Chest pain (if active heart problem)
- Exacerbation of heart failure

Neutropenia
- Active infection
- At risk of infection

Thrombocytopenia
- Petechiae
- Risk of bleeding
MDS — CBC

- **White Blood Cell**: Important to see the differential
  - Rising WBC, especially with “BLASTS” could indicate transition to more aggressive MDS or AML
  - Low WBC, especially Neutrophils below 1000 can increase risk of infection,
- **Hemoglobin**: below 10 can cause symptoms, below 7-8 may require transfusion in symptomatic patients
- **Platelets** between 20,000-100,000 (20-100) generally no intervention offered but be careful of trauma as bleeding risk increases at lower levels
Making the Diagnosis
Low blood counts(s):
- Hb <11 g/dL, or
- ANC <1500/μL, or
- Platelets <100 x 10⁹L

MDS “decisive” criteria:
- >10% dysplastic cells in 1 or more cell lineages, or
- 5-19% blasts, or
- Abnormal karyotype typical for MDS, or
- Evidence of clonality (by FISH or another test)

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.)
Classification of MDS Subtypes
• Pathologist, clinicians communicate that they are diagnosing, treating and studying the same disease
### Changes in World Health Organization MDS categories (2016)

<table>
<thead>
<tr>
<th>2008 Name</th>
<th>Abbrev</th>
<th>2016 Name</th>
<th>Abbrev</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refractory cytopenia with unilineage dysplasia</td>
<td>RCUUD (includes RA,RN, RT)</td>
<td>MDS with single lineage dysplasia</td>
<td>MDS-SLD</td>
</tr>
<tr>
<td>Refractory anemia with ringed sideroblasts</td>
<td>RARS</td>
<td>MDS with ringed sideroblasts</td>
<td>MDS-RS</td>
</tr>
<tr>
<td>MDS with isolated 5q</td>
<td>Del (5q)</td>
<td>unchanged</td>
<td>unchanged</td>
</tr>
<tr>
<td>Refractory cytopenia with multilineage dysplasia</td>
<td>RCMD</td>
<td>MDS with multilineage dysplasia</td>
<td>MDS-MLD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(with ringed sideroblasts*)</td>
<td>MDS-RS-MLD</td>
</tr>
<tr>
<td>Refractory anemia with excess blasts type 1</td>
<td>RAEB-1</td>
<td>MDS with excess blasts, type 1</td>
<td>MDS-EB-1</td>
</tr>
<tr>
<td>Refractory anemia with excess blast type 2</td>
<td>RAEB-2</td>
<td>MDS with excess blast, type 2</td>
<td>MDS-EB-2</td>
</tr>
<tr>
<td>MDS, unclassifiable</td>
<td>MDS-U</td>
<td>unchanged</td>
<td>unchanged</td>
</tr>
<tr>
<td>Refractory cytopenia(s) of childhood</td>
<td>RCC</td>
<td>unchanged</td>
<td>unchanged</td>
</tr>
</tbody>
</table>

Now includes <15% sideroblasts if SF3B1 mutation is present

*WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues, 4th edition.*
## Genetic Abnormalities in MDS

<table>
<thead>
<tr>
<th>Translocations / Rearrangements</th>
<th>Uniparental disomy / Microdeletions</th>
<th>Copy Number Change</th>
<th>Point Mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rare in MDS:</td>
<td>Rare - often at sites of point mutations:</td>
<td>About 50% of cases:</td>
<td>Most common:</td>
</tr>
<tr>
<td>t(6;9)</td>
<td>4q TET2</td>
<td>del(5q)</td>
<td>Likely in all cases</td>
</tr>
<tr>
<td>i(17q)</td>
<td>7q EZH2</td>
<td>-7/del(7q)</td>
<td></td>
</tr>
<tr>
<td>t(1;7)</td>
<td>11q CBL</td>
<td>del(20q)</td>
<td>~90% of cases have mutations in a known gene</td>
</tr>
<tr>
<td>t(3;?)</td>
<td>17p TP53</td>
<td>del(17p)</td>
<td></td>
</tr>
<tr>
<td>t(11;?)</td>
<td></td>
<td>del(11q)</td>
<td></td>
</tr>
<tr>
<td>inv(3)</td>
<td></td>
<td>del(12p)</td>
<td></td>
</tr>
<tr>
<td>idic(X)(q13)</td>
<td></td>
<td>+8</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>-Y</td>
<td></td>
</tr>
</tbody>
</table>

### Observed Frequency in MDS
Point Mutations in MDS

Tyrosine Kinase Pathway
- JAK2
- KRAS
- BRAF
- NRAS
- RTK’s
- PTPN11
- CBL

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

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

Others
- TP53
- NPM1
- CALR
- BRCC3
- GNAS/GNB1
- BCOR
- NPM1
- Cohesins

Splicing Factors
- SF3B1
- U2AF1
- ZRSF2
- SRSF2
- SF1
- SF3A1
- PRPF40B
- PRPF8
- U2AF2

Slide borrowed from Dr. Rafael Bejar
Prognostic Risk Assessment
If all of the MDS patients diagnosed in the U.S. this year were represented as 100 people...

6 will undergo allogeneic transplant: 2 will be cured, 3 will relapse and die, 1 will die of a complication such as GVHD

12 will die of hemorrhage

20 will die of infection

7 will die of anemia-related complications (CVA, MI etc)

24 will progress to AML; of the subset who will receive intensive therapy followed by transplant, 2 will survive

29 will die of unrelated causes (e.g., geriatric conditions)
What does this mean for me?

• Your doctor can use simple clinical information from your blood and bone marrow tests to give you SOME IDEA how long your disease is likely to remain stable

• This information is useful in helping choose therapies
### IPSS-R

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Categories and Associated Scores</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytogenetic risk group</td>
<td>Very good</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Marrow blast proportion</td>
<td>≤2%</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt; 2% to &lt;5%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>5% to 10%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;10%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>≥10</td>
<td>0</td>
<td>1</td>
<td></td>
<td>1.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>8 to &lt;10</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;8</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelet count (x 10⁹/L)</td>
<td>≥100</td>
<td>0</td>
<td>0.5</td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>50 to &lt;100</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;50</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absolute neutrophil count (x 10⁹/L)</td>
<td>≥0.8</td>
<td>0</td>
<td>0.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;0.8</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Possible range of summed scores: 0-10

# Cytogenetics - 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><strong>Very good</strong></td>
<td>del(11q), -Y</td>
<td>60.8</td>
<td>2.9%</td>
</tr>
<tr>
<td><strong>Good</strong></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><strong>Intermediate</strong></td>
<td>+8, del(7q), i(17q), +19, +21, any single or double abnormality not listed, 2 or more independent clones</td>
<td>26.1</td>
<td>19.2%</td>
</tr>
<tr>
<td><strong>Poor</strong></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><strong>Very poor</strong></td>
<td>Complex with &gt; 3 abnormalities</td>
<td>5.9</td>
<td>6.8%</td>
</tr>
</tbody>
</table>

## IPSS-R

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Points</th>
<th>% of Patients</th>
<th>Median Survival, years</th>
<th>Time Until 25% of Patients Develop 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 to 3</td>
<td>38</td>
<td>5.3</td>
<td>10.8</td>
</tr>
<tr>
<td>Intermediate</td>
<td>&gt;3 to 4.5</td>
<td>20</td>
<td>3.0</td>
<td>3.2</td>
</tr>
<tr>
<td>High</td>
<td>&gt;4.5 to 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 IPSS-R

- Roughly half of patients have relevant cytogenetic abnormalities
- Heterogeneity remains within each risk category, particularly the lower-risk categories.
- Excludes therapy-related MDS and CMML
- Is only validated at the time of initial diagnosis in untreated patients
- Cannot be applied during the course of disease

The IPSS’s do not include mutational data
30% of MDS patients have a mutation in one of these genes

These mutations indicate more severe disease!

Impact of Mutations by IPSS Group

Pretreatment, patient self reported fatigue in high risk MDS provide important information about the severity of the disease
How Long Did It Take to Get an MDS Diagnosis?

First abnormal blood test

3 years

Diagnosis of MDS

Sekeres et al. ASH 2009; abstract 1771.
How Doctors First Describe MDS

- Bone marrow disorder: 80%
- Anemia: 56%
- Blood disorder: 32%
- Neutropenia: 19%
- Thrombocytopenia: 17%
- Syndrome: 15%
- Other: 7.50%
- Cancer: 7%
- Leukemia: 6%
- Hematologic malignancy: 4%
What’s My Risk?

IPSS Risk Score

- Low risk: 13%
- Int-1: 18%
- Int-2: 11%
- High: 4%
- Don't know: 55%

Sekeres et al. ASH 2009; abstract 1771
Risk Adapted Therapy
Goals of Treatment

• If possible, cure me

• If you can't cure me, at least make me live longer and feel better

• If you can't make me live longer at least make me feel better

• If you can't make me feel better, get me another doctor
Treatment Considerations

• Disease characteristics
  – Goals of therapy
  – Using low intensity treatment for low risk disease vs Intense therapy

• Treatment administrative characteristics

• Treatment pharmacology characteristics
  – Therapy can initially worsen patients’ clinical condition
  – Avoid discontinuation of therapy before achieving benefit

• Patient characteristics
  – Age and frailty are relative but organs do have chronologic age

• Expectation management
  – Adverse events usually decrease in frequency as therapy continues
  – Treatment plans are created by mutual discussions
Treatment Options for MDS

Observation
- Erythropoiesis stimulating agents
- Granulocyte colony stimulating factor
- Iron chelation
- Red blood cell transfusion
- Platelet transfusion
- Lenalidomide
- Immunosuppression
- Hypomethylating agent
- Stem cell transplantation

Intensity

Clinical Trials – always the best option
Treating Lower Risk MDS

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.
Role of Transfusions

- Usually order Leukoreduced blood products.
- Can be life-saving, life-prolonging
- Platelets live about 7 days
  - 1 unit bump the platelets up by 20-30,000
  - Irradiated Platelets can have short life

- Red Blood Cells live from 7-28 days on average
  - 1 unit bumps the hemoglobin 1 point
  - Ongoing transfusion of red cells can lead to iron overload
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!
Primary Goal: to improve QUALITY OF LIFE

- Red blood cell growth factors
- Erythropoiesis Stimulating Agents (ESAs)
  - Darbepoetin alfa (Aranesp)
  - Epoetin alfa (Procrit, Epogen)
Erythropoietin

- Anemia leads to decreased oxygen to kidneys
- Increased red cell production
- Erythropoietin
**Erythropoiesis Stimulating Agents**

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

- **ESAs** – act like our own erythropoietin
- **TPO mimetics**
- **G-CSF** (neupogen)

### 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>= +2 pts</td>
</tr>
<tr>
<td>100-500</td>
<td>= +1 pt</td>
</tr>
<tr>
<td>&gt;500</td>
<td>= -3 pts</td>
</tr>
<tr>
<td>&lt;2 Units / month</td>
<td>= +2 pts</td>
</tr>
<tr>
<td>≥2 Units / month</td>
<td>= -2 pts</td>
</tr>
</tbody>
</table>

### Total Score

<table>
<thead>
<tr>
<th>Response Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>High likelihood of response: &gt; +1</td>
</tr>
<tr>
<td>Intermediate likelihood: -1 to +1</td>
</tr>
<tr>
<td>Low likelihood of response: &lt; -1</td>
</tr>
</tbody>
</table>

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Permitted to use from Dr. Bejar

Hellstrom-Lindberg E et al *Br J Haem* 2003; 120:1037
Majority of responses occur within 8-12 weeks
  – Trend Reticulocytes may help to see response
  – IPSS –R low and very low likely to response
  – EPO* in solid tumor patients showed increased heart attacks, stroke, heart failure, blood clots, increased tumor growth, death, especially when hgb >12

Thrombotic events are rare provided Hgb level are controlled

 Interruption of treatment almost constantly provokes loss of response

 NOT FDA approved; major effects on insurance coverage

Primary Goal: to improve QUALITY OF LIFE

ESAs can be combined with G-CSF
- response rate of 46.6%, EPO <200 and <5% blasts predictive

ESAs can be combined with Lenalidomide
- response rate of 31% to Len, 52% to both. TI 18.4% vs. 32.0%!

ESAs can be combined with Azacitidine – not yet standard
Epo + G-CSF → Synergy

81 year old female diagnosed with MDS-RARS

Bimonthly PRBC Transfusions
**Thrombopoietin Mimetics**

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

- Eltrombopag (Oral) & Romiplostim SC – approved, but not in MDS

Initial concern about increasing blasts and risk of AML

Follow-up suggests Romiplostim safe in lower risk patients

Mittleman M et al *ASH Abstracts*, 2013. Abstract #3822

Kantarjian H et al *ASH Abstracts*, 2013. Abstract #421
What my next most effective therapy?

- Immunosuppression

Who is likely to respond

- Hypoplastic bone marrow (too few cells)
- PNH clones
- Certain immune receptor types (HLA-DR15)
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

Who are likely to response:
- hypocellular aspirate
- lower blast %
- younger age
- more recent diagnosis

Low dose Azacitidine or Decitabine:

<table>
<thead>
<tr>
<th>Response, n (%)</th>
<th>Low dose AZA or DEC</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>36</td>
</tr>
<tr>
<td>Hematologic improvement</td>
<td>14</td>
</tr>
<tr>
<td>Molecular CR</td>
<td>9</td>
</tr>
<tr>
<td>Overall Response rate</td>
<td>59</td>
</tr>
<tr>
<td>SD</td>
<td>34</td>
</tr>
<tr>
<td>PD</td>
<td>7</td>
</tr>
</tbody>
</table>

Hypomethylating Agents
Lenalidomide

Proportion of patients with RBC-TI ≥ 8 weeks:
- LEN (n = 41):
  - 90%, 4 cycles
  - 66%, 3 cycles
  - 44%, 2 cycles
  - 37%, 1 cycle
- Placebo (n = 1):
  - 0%

More likely to respond after Epo failure and if Epo level is less than 500:
- 35.1% vs 23.1% vs 8.6% without prior Epo use

Primary Goal: to improve QUALITY OF LIFE

Is a combination of LEN +/- ESA likely to work? In non-del(5q) MDS patients:

- **Toma et al, Leukemia. 2016 Apr;30(4):897-905**
The MEDALIST Trial: Results of a Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of Luspatercept to Treat Patients With Very Low-, Low-, or Intermediate-Risk Myelodysplastic Syndromes (MDS) Associated Anemia With Ring Sideroblasts (RS) Who Require Red Blood Cell (RBC) Transfusions

**MEDALIST Trial**

**Study Design – A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study**

**Patient Population**
- MDS-RS (WHO): ≥ 15% RS or ≥ 5% with SF3B1 mutation
- < 5% blasts in bone marrow
- No del(5q) MDS
- IPSS-R Very Low-, Low-, or Intermediate-risk
- Prior ESA response
  - Refractory, intolerant
  - ESA naive: EPO > 200 U/L
- Average RBC transfusion burden ≥ 2 units/8 weeks
- No prior treatment with disease-modifying agents (e.g. iMIDs, HMAs)

**Randomize 2:1**

**Luspatercept 1.0 mg/kg (s.c.) every 21 days**
- n = 153
- Dose titrated up to a maximum of 1.75 mg/kg

**Placebo (s.c.) every 21 days**
- n = 76

**Disease & Response Assessment week 24 & every 6 months**
- Treatment discontinued for lack of clinical benefit or disease progression per IWG criteria; no crossover allowed

**Subjects**
- Followed ≥ 3 years post final dose for AML progression, subsequent MDS treatment and overall survival

Data cutoff: May 8, 2018 includes last subject randomized + 48 weeks.

EPO, erythropoietin; HMA, hypomethylating agent; iMID, immunomodulatory drug; IWG, International Working Group; s.c., subcutaneously; SF3B1, splicing factor 3b subunit 1; WHO, World Health Organization.
• 153 Patients **Luspatercept** 1mg/kg SC every 21 days
  – **38%** achieved transfusion-independence at 8 weeks
  – 28% achieved transfusion-independence at 12 weeks

• 76 Patients Placebo
  – 13% achieved transfusion-independence at 8 weeks
  – 8% achieved transfusion-independence at 8 weeks
MEDALIST Trial
Duration of RBC-TI Response in Primary Endpoint Responders

Median duration (weeks) (95% CI): 30.6 (20.6–40.6) vs 13.6 (9.1–54.9)

Duration of RBC-TI (week)

Probability of Maintaining RBC-TI

Number of patients
Luspatercept 58 49 37 29 22 18 10 6 3 2 1 1 0
Placebo 10 9 3 2 2 2 0

During indicated treatment period. Patients who maintained RBC-TI at the time of analysis are censored.
Imetelstat Treatment Leads to Durable Transfusion Independence in RBC Transfusion-Dependent, Non-Del(5q) Lower Risk MDS Relapsed/Refractory to Erythropoiesis-Stimulating Agent Who Are Lenalidomide and HMA Naive

David P. Steensma, MD¹, Uwe Platzbecker, MD², Koen Van Eygen, MD³, Azra Raza, MD⁴, Valeria Santini, MD⁵, Ulrich Germing, MD, PhD⁶, Patricia Font, MD⁷, Irina Samarina, MD⁸, Maria Díez-Campelo, MD, PhD⁹, Sylvain Thepot, MD¹⁰, Edo Vellenga, MD¹¹, Mrinal M. Patnaik, MD, MBBS¹², Jun Ho Jang, MD, PhD¹³, Jacqueline Bussolari, PhD¹⁴, Laurie Sherman, BSN¹⁴, Libo Sun, PhD¹⁴, Helen Varsos, MS, RPh¹⁴, Esther Rose, MD¹⁴ and Pierre Fenaux, MD, PhD¹⁵

¹Dana-Farber Cancer Institute (US), ²University Hospital Carl Gustav Carus, Dresden (DE), ³Algemeen Ziekenhuis Groeninge, Kortrijk (BE), ⁴Columbia University Medical Center (US), ⁵MDS Unit, AOU Careggi-University of Florence (IT), ⁶Heinrich-Heine-Universität, Düsseldorf (DE), ⁷Hospital General Universitario Gregorio Marañon, Madrid (ES), ⁸Emergency Hospital of Dzerzhinsk, Nizhny Novgorod (RU), ⁹The University Hospital of Salamanca (ES), ¹⁰CHU Angers (FR), ¹¹University Medical Center Groningen (NE), ¹²Mayo Clinic, Rochester (US), ¹³Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul (KO), ¹⁴Janssen Research & Development, LLC (US), ¹⁵Hôpital Saint-Louis, Université Paris (FR)
• 38 Patients received Imetelstat 7.5 mg/kg IV every 4 weeks
  – 37% achieved transfusion-independence at 8 weeks
  – 26% achieved transfusion-independence at 24 weeks
  – Median time to onset of transfusion Independence 8 weeks
  – Median duration of TI not reached

  – Neutropenia and thrombocytopenia in 20-25%
Iron Balance and Transfusions

3-4 grams of Iron in the body

Daily intake
1.5 mg (0.04%)
Tightly regulated

Every three units of blood

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

Permission to use from Dr. Bejar
Iron Chelation

Three ways are FDA approved:

Deferoxamine (Desferal) – subcutaneous pump 8-12 hrs/day

Deferasirox (Exjade or Jadenu) – oral suspension or Tablet

Deferiprone (Ferriprox) – oral pill form – 3x per day

But side effects and adverse events can be significant!

At this point not commonly used in high risk disease

Deferasirox – renal, hepatic failure and GI bleeding

Deferiprone – agranulocytosis (no neutrophils!)
More transfusions and elevated ferritin levels are associated with poor outcomes in MDS patients.

Is high iron level has independent effect 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%).

We consider treatment in lower risk, transfusion dependent patients with long life expectancy after 20+ transfusions.

Emanuele Angelucci, Junmin Li, Peter Greenberg, Depei Wu, Ming Hou, Efreen Horacio Montaño Figueroa, Maria Guadalupe Rodriguez, Xunwei Dong, Jagannath Ghosh, Miguel Izquierdo, and Guillermo Garcia-Manero

1Hematology and Transplant Center, IRCCS Ospedale Policlinico San Martino, Genova, Italy; 2Ruijin Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai, China; 3Stanford University Medical Center, Stanford, CA, USA; 4Jiangsu Institute of Hematology, First Affiliated Hospital of Soochow University, Suzhou, China; 5Department of Hematology, Qilu Hospital, Shandong University, Jinan, China; 6Department of Hematology, Hospital General de México, Mexico City, Mexico; 7Department of Hematology, Hospital de Especialidades, Centro Médico Nacional La Raza, IMSS, Mexico City, Mexico; 8Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA; 9Novartis Pharma AG, Basel, Switzerland; 10MD Anderson Cancer Center, University of Texas, Houston, TX, USA
### Primary endpoint EFS:

<table>
<thead>
<tr>
<th>All patients*</th>
<th>Log-rank test</th>
<th>Cox model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Event/N (%)</td>
<td>Median time to event (95% CI), days†</td>
</tr>
<tr>
<td>Deferasirox</td>
<td>62/149 (41.6)</td>
<td>1440 (1167, 1559)</td>
</tr>
<tr>
<td>Placebo</td>
<td>37/76 (48.7)</td>
<td>1091 (820, 1348)</td>
</tr>
</tbody>
</table>

*Both the log-rank test and Cox proportional hazards model were stratified by stratification factors; †Median time to event and 95% CI generated by Kaplan–Meier estimation; ‡Exploratory P value is one tailed and based on the stratified log-rank test; §Based on a Wald test from the Cox model

A **36.4%** risk reduction in EFS was observed in the deferasirox arm compared with the placebo arm (HR: 0.636; 95% CI: 0.42, 0.96; nominal P=0.015)
### Summary of overall survival

The table below summarizes the overall survival data for patients treated with Deferasirox and Placebo.

<table>
<thead>
<tr>
<th></th>
<th>Log-rank test</th>
<th>Cox model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Event/N (%)</td>
<td>Median time (95% CI),</td>
</tr>
<tr>
<td></td>
<td></td>
<td>days†</td>
</tr>
<tr>
<td></td>
<td></td>
<td>P value‡</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hazard ratio (95% CI)§</td>
</tr>
<tr>
<td>Deferasirox</td>
<td>57/149 (38.3)</td>
<td>1907 (1440, NE)</td>
</tr>
<tr>
<td>Placebo</td>
<td>33/76 (43.4)</td>
<td>1509 (1095, 1804)</td>
</tr>
</tbody>
</table>

*Both log-rank test and Cox proportional hazards model were stratified by stratification factors; †Median time to event and 95% CI generated by Kaplan–Meier estimation; ‡Exploratory P value is one-tailed and based on the stratified log-rank test; §Based on a Wald test from the Cox model.

Following study drug discontinuation 52.1% of placebo patients started ICT.
Guidelines for Lower Risk MDS

1. Do I need to treat? - symptomatic cytopenias
2. Is LEN likely to work? - del(5q)
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, or Lenalidomide, Epo +Lena
7. ? Luspatercept ? Imetelstat
8. Consider HSCT or clinical trial!
Guidelines for Lower Risk MDS

Special Considerations:

Transfusion Dependence
- Indication for treatment – even with AZA/DEC, consider chelation

Del(5q)
- High response rate to LEN even if other abnormalities

Serum EPO level
- Used to predict EPO response, > 500 → unlikely to work

Indication for G-CSF
- used to boost EPO, not for primary neutropenia

Immunosuppressive Therapy
- ≤ 60y, hypocellular marrow, HLA-DR15+, PNH clone
Overview of High Risk

• Refining Prognosis and ‘High’ Risk

• Advances in Stem Cell Transplantation
What does high risk mean

- Worsening blood counts
- Transformation to acute leukemia
- Bone marrow failure
Current Therapies
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%

Azacitididine Response:

ORR: ~50%

CR: ~17%

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

![Graph showing Hgb (G/DL) over cycle numbers. The graph indicates an increase in Hgb levels over cycles, with a notable peak toward the end.]
Decitabine Phase III Trial
Dosed q8h x 3 days per 28 days
CR: 17%
CR+PR: 30%

ADOPT Trial and 3-Schedule Trial
Dosed q24h x 5 days per 28 days
CR: 17%
CR+PR: 32%

ORR: 52% (+ heme response)
Best response: 50% at 2 cycles

Major Toxicity:
Neutropenia: 31% (FeverN 11%)
Thrombocytopenia: 18%
Azacitidine and Decitabine

Therapy can initially worsen patients’ clinical condition

Avoid discontinuation of therapy before achieving benefit, Slow Responses can take 4-6 months to appear

Continuous Treatment – 5 to 7 days every 4 weeks

Generally well tolerated

- No hair loss or mucositis
- Little to no nausea or vomiting
- Common side effects are fatigue and constipation (Zofran ?)
Oral Decitabine

Key Eligibility Criteria*: MDS and CMML patients eligible for treatment with IV decitabine as per the FDA approved label

Cycle 1: ASTX727 tablet
Cycle 2: IV Decitabine
Cycle ≥3*: ASTX727 tablet

Cycle 1: IV Decitabine
Cycle 2: ASTX727 tablet
Cycle ≥3*: ASTX727 tablet

Treatment, ASTX727 or decitabine, is given daily x5 every 28 days per cycle.
**IDH Mutations as a Target in MDS**

- IDH are critical enzymes of the citric acid cycle
- Mutant IDH2 (mIDH2) produces 2-HG, which alters DNA methylation, blocks cellular differentiation
- mIDH2 in ~5% of MDS
- Enasidenib (AG-221/CC-90007) - selective, oral, potent inhibitor of mIDH2 enzyme
- Objective: safety and efficacy of enasidenib in mIDH2 MDS


Stein et al. ASH 2016; abstract 343
### Response and time on therapy

<table>
<thead>
<tr>
<th>Overall response rate (CR + PR + mCR + HI)</th>
<th>MDS Patients (N=17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>10/17 (59)</td>
</tr>
</tbody>
</table>

### Best Response

<table>
<thead>
<tr>
<th>Category</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete remission</td>
<td>1/11 (9)</td>
</tr>
<tr>
<td>Partial remission</td>
<td>1/11 (9)</td>
</tr>
<tr>
<td>Marrow CR</td>
<td>3/11 (27)</td>
</tr>
<tr>
<td>Any hematologic improvement (HI)†</td>
<td>5/17 (29)</td>
</tr>
<tr>
<td>HI-E</td>
<td>3/15 (20)</td>
</tr>
<tr>
<td>HI-P</td>
<td>4/12 (33)</td>
</tr>
<tr>
<td>HI-N</td>
<td>4/10 (40)</td>
</tr>
</tbody>
</table>

Stein et al. ASH 2016; abstract 343
Phase 1b/2 Combination Study of APR-246 and Azacitidine (AZA) in Patients with TP53 Mutant Myelodysplastic Syndromes (MDS) and Acute Myeloid Leukemia (AML)

David A Sallman¹, Amy DeZern², David P Steensma³, Kendra Sweet¹, Thomas Cluzeau⁴, Mikkael Sekkeres⁵, Guillermo Garcia-Manero⁶, Gail Roboz⁷, Amy McLemore¹, Kathy McGraw¹, John Puskas¹, Ling Zhang¹, Chirag Bhagat⁸, Jiqiang Yao⁹, Najla H Al Ali¹, Eric Padron¹, Roger Tell¹⁰, Jeffrey E. Lancet¹, Pierre Fenaux¹¹, Alan F List¹ and Rami S Komrokji¹

¹Malignant Hematology Department, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL, USA.; ²Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University, Baltimore, MD, USA; ³Department of Medical Oncology, Dana Farber Cancer Institute, Harvard Medical School, Boston, MA, USA; ⁴Cote D’azur University, Nice Sophia Antipolis University, Hematology Department, CHU Nice, Nice, France; ⁵Department of Hematology and Medical Oncology, Cleveland Clinic, Cleveland, OH, USA; ⁶Department of Leukemia, MD Anderson Cancer Center, Houston, TX, USA; ⁷Weill Cornell Medical College, New York, NY, USA; ⁸Cancer Informatics Core, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL, USA; ⁹Aprea Therapeutics, Stockholm, Sweden; ¹⁰Hospital St Louis, Paris 7 University, Paris, France.

2018 ASH Abstract # 3091
## Treatment Response

<table>
<thead>
<tr>
<th>Best Response at Cutoff</th>
<th>Ph1b</th>
<th>Ph2</th>
<th>MDS</th>
<th>AML</th>
<th>All</th>
<th>AZA Historical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evaluable Patients</td>
<td>11</td>
<td>9</td>
<td>15</td>
<td>5</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td><strong>Response Rate</strong></td>
<td>100%</td>
<td>89%</td>
<td>93%</td>
<td>100%</td>
<td>95%</td>
<td>30-50%</td>
</tr>
<tr>
<td><strong>CR Rate</strong></td>
<td>82%</td>
<td>56%</td>
<td>67%</td>
<td>80%</td>
<td>70%</td>
<td>20-30%</td>
</tr>
</tbody>
</table>
Guidelines for Higher Risk MDS

Goal: to improve LIFE EXPECTANCY & QUALITY OF LIFE

Special Considerations:

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

Don’t Ignore 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

<table>
<thead>
<tr>
<th>Reasons for “failure” in azacitidine study</th>
</tr>
</thead>
<tbody>
<tr>
<td>9% didn’t tolerate AZA (69% were not responding, 31% had an initial response)</td>
</tr>
<tr>
<td>55% primary failure (progression in 60%, stable disease without response in 40%)</td>
</tr>
<tr>
<td>36% secondary failure after initial response (best response: CR 20%, PR 7%, HI 73%)</td>
</tr>
</tbody>
</table>

### Outcomes after failure

- Median overall survival for whole cohort post-AZA: **5.6 months**
- 2 year survival: **15%**

Favorable factors: **female, younger (<60), better risk karyotype, <10% blasts, some response to azacitidine**

Comparison to decitabine failures @ MDACC: **median survival 4.3 months**, n=87

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Slide borrowed from Dr. David Steensma
Stem Cell Transplantation
Goals of Transplantation

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

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

Donor Cells

Conditioning  Engraftment  Graft-vs.-MDS

Permitted to use from Dr. Bejar
AGE DISTRIBUTION OF PATIENTS WITH MDS

Patients with MDS

Patients transplanted for MDS
The Decision – Whether and When

HIGH RISK MDS STANDARD RISK OF TRANPLANT RELATED DEATH
The Decision – Whether and When

LOW RISK MDS HIGH RISK OF TRANPLANT RELATED DEATH

SURVIVAL, %

TIME
<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! (40-45%)
- Survives transplant; MDS recurs/persists (22-30%)
- Dies from complication of transplant (20-25%)


Slide borrowed from Dr. David Steensma
Transplant is curative therapy that offers survival advantage when applied at an optimal point.

In pts who are eligible for transplant there is no difference in survival for pt 55-64 compared to pts 65 yrs and older.

Age is not itself a contraindication – but comorbidities that accompany age in some people can be.
Take home messages

- Ask if the diagnosis is right?
- Ask your risk category
- Risk category is important to set GOALS of therapy
- Quality of life is important goal of treatment in MDS
- Be aware about risk of infections
- Allogeneic transplantation can be curative
- Clinical Trials