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 (12-14)
- **Platelets**: 250,000
Questions

• What do I have?

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

- Vitamin B12 deficiency
- Copper deficiency
- Alcohol abuse
- Iron deficiency
- Thyroid disorder
- Anemia of CKD
- Anemia of chronic disease
- MDS
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

Blasts

Normal

Red
Platelets
White

Slide borrowed 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
MDS – Let’s build a definition

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

US SEER Cancer Registry Data

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

<table>
<thead>
<tr>
<th>Environmental</th>
<th>Inborn</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AGING</strong></td>
<td><strong>Fanconi anemia</strong></td>
</tr>
<tr>
<td>Exposure to <strong>DNA alkylating agents</strong> <em>(chlorambucil, melphalan, cyclophosphamide)</em></td>
<td>Familial Platelet Disorder with AML Predisposition (“FPD-AML”) <em>(RUNX1, CEBPA)</em></td>
</tr>
<tr>
<td>Exposure to <strong>topoisomerase II inhibitors</strong> <em>(etoposide, anthracyclines)</em></td>
<td><strong>GATA2</strong> mutant <em>(MonoMACsyndrome: monocytopenia, B/NK lymphopenia, atypical mycobacteria and viral and other infections, pulmonary proteinosis, neoplasms)</em></td>
</tr>
<tr>
<td>Exposure to <strong>ionizing radiation</strong></td>
<td>Other congenital marrow failure syndromes or DNA repair defects <em>(Bloom syndrome, ataxia-telangiectasia, etc.)</em></td>
</tr>
<tr>
<td>Environmental / occupational exposures <em>(hydrocarbons etc.)</em></td>
<td>Familial syndromes of unknown origin</td>
</tr>
<tr>
<td><strong>Antecedent acquired hematological disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Aplastic anemia <em>(15-20%)</em></td>
<td></td>
</tr>
<tr>
<td>PNH <em>(5-25%)</em></td>
<td></td>
</tr>
</tbody>
</table>

Slide borrowed from Dr. David Steensma
Genetics - Mutations
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
Myelodysplastic Syndromes

- Incidence rises with age (mean age 71)
  - 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?)
- Afflicts 15,000 – 45,000 people annually
Signs and Symptoms

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

Neutropenia (Low Neutrophils- Type of White Blood Cells)
- Active infection
- At risk of infection

Thrombocytopenia (Low Platelet Counts)
- Bruising
- Risk of bleeding
Making the Diagnosis
Cytopenia(s):
- Hb <11 g/dL, or
- ANC <1500/μL, or
- Platelets <100 x 10⁹L

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 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.)

Permitted to use from Dr. David Steensma
Myelodysplastic Syndromes (MDS)

- Aplastic Anemia
- Paroxysmal Nocturnal Hemoglobinuria
- Pure Red cell Aplasia
- T-LGL
- Fanconi Anemia
- Acute Myeloid Leukemia (AML)
- Myeloproliferative Neoplasms
Classification of MDS Subtypes
• Pathologist, clinicians communicate that they are diagnosing, treating and studying the same disease
<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 (with ringed sideroblasts*)</td>
<td>MDS-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>~90% of cases have mutations in a known gene</td>
</tr>
<tr>
<td>t(1;7)</td>
<td>11q CBL</td>
<td>del(20q)</td>
<td></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>
Point Mutations in MDS

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

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

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

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

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

Slide borrowed from Dr. Rafel 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)
• 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>
</tr>
</thead>
<tbody>
<tr>
<td>Cytogenetic risk group</td>
<td>Very good, Good, Intermediate, Poor, Very Poor</td>
</tr>
<tr>
<td>Marrow blast proportion</td>
<td>≤2%, &gt;2% to &lt;5%, 5% to 10%, &gt;10%</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>≥10, 8 to &lt;10, &lt;8</td>
</tr>
<tr>
<td>Platelet count (x 10^9/L)</td>
<td>≥100, 50 to &lt;100, &lt;50</td>
</tr>
<tr>
<td>Absolute neutrophil count (x 10^9/L)</td>
<td>≥0.8, &lt;0.8</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>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, 2 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>

## 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>

- 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

The IPSS’s do not include mutational data
Impact of Mutations by IPSS Group

Bejar et al. NEJM. 2011;364:2496-506.
How Long Did It Take to Get an MDS Diagnosis?

- First abnormal blood test
- Diagnosis of MDS

3 years
How Doctors First Describe MDS

- Bone marrow disorder: 80%
- Anemia: 56%
- Blood disorder: 32%
- Neutropenia: 19%
- Thrombocytopenia: 17%
- Syndrome: 15%
- Other: 7.5%
- 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

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.
Treating Lower Risk MDS

• Transfusions
• 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
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!
Primary Goal: to improve QUALITY OF LIFE

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

Anemia leads to decreased oxygen to kidneys

Increased Red cell production

Erythropoeitin
Erythropoiesis Stimulating Agents

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>-3 pts</td>
</tr>
</tbody>
</table>

Total Score

<table>
<thead>
<tr>
<th>Response Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>74% (n=34)</td>
</tr>
<tr>
<td>23% (n=31)</td>
</tr>
<tr>
<td>7% (n=39)</td>
</tr>
</tbody>
</table>

Hellstrom-Lindberg E et al *Br J Haem* 2003; 120:1037

Permitted to use from Dr. Bejar
Growth factor in Low risk disease

- 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

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) & Romiplostitim SC – approved, but not in MDS

Initial concern about increasing blasts and risk of AML

Follow-up suggests Romiplostitim safe in lower risk patients

Mittleman M et al ASH Abstracts, 2013. Abstract #3822
Kantarjian H et al ASH Abstracts, 2013. Abstract #421
Primary Goal: to improve **QUALITY OF LIFE**

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)
Primary Goal: to improve QUALITY OF LIFE

Swiss/German Phase III RCT of ATG + Cyclosporin (88 patients)

CR+PR: 29%

No effect on survival

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

Inhibitors of DNA methyl transferases:

<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>ORR</td>
<td>59</td>
</tr>
<tr>
<td>SD</td>
<td>34</td>
</tr>
<tr>
<td>PD</td>
<td>7</td>
</tr>
</tbody>
</table>
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)

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

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, HMA)

### Randomize 2:1
- Luspatercept 1.0 mg/kg (s.c.) every 21 days
  - Dose titrated up to a maximum of 1.75 mg/kg
  - n = 153
- 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.
**MEDALIST Trial**  
**Primary Endpoint: Red Blood Cell Transfusion Independence ≥ 8 Weeks**

<table>
<thead>
<tr>
<th>RBC-TI ≥ 8 weeks</th>
<th>Luspatercept (n = 153)</th>
<th>Placebo (n = 76)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weeks 1–24, n (%)</td>
<td>58 (37.9)</td>
<td>10 (13.2)</td>
</tr>
<tr>
<td>95% CI</td>
<td>30.2–46.1</td>
<td>6.5–22.9</td>
</tr>
<tr>
<td>(P) value(^a)</td>
<td>(&lt; 0.0001)</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) Cochran–Mantel–Haenszel test stratified for average baseline RBC transfusion requirement (≥ 6 units vs < 6 units of RBCs/8 weeks) and baseline IPSS-R score (Very Low or Low vs Intermediate).  
CI, confidence interval.
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)

Number of patients

<table>
<thead>
<tr>
<th>Luspatercept</th>
<th>58</th>
<th>49</th>
<th>37</th>
<th>29</th>
<th>22</th>
<th>18</th>
<th>10</th>
<th>6</th>
<th>3</th>
<th>2</th>
<th>1</th>
<th>1</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>10</td>
<td>9</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

*During indicated treatment period. Patients who maintained RBC-TI at the time of analysis are censored.*
Iron Balance and Transfusions

- **Daily intake**
  - 1.5 mg (0.04%)
  - Tightly regulated

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

- **3-4 grams of Iron in the body**

- **Every three units of blood**
Iron Balance and Transfusions

Daily intake:
1.5 mg (0.04%)
Tightly regulated

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

Every three units of blood

3-4 grams of Iron in the body

Permitted to use from Dr. Bejar
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.

Is high iron level has independent effect or just reflective of disease?

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

Recent trial showed 36% reduction in terms of events in low risk patients without survival benefit

Primary Goal: to improve QUALITY OF LIFE

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
7. 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%

Azacitidine Response:

ORR: ~50%

CR: ~17%

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

Hgb (G/DL) vs. Cycle
Decitabine

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% (FN 11%)
Thrombocytopenia: 18%
Oral Decitabine

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

1:1 Randomization

- Cycle 1: ASTX727 tablet
- Cycle 2: IV Decitabine
- 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* (m*IDH2*) produces 2-HG, which alters DNA methylation, blocks cellular differentiation

- m*IDH2* in ~5% of MDS
- Enasidenib (AG-221/CC-90007) - selective, oral, potent inhibitor of m*IDH2* enzyme


Stein et al. ASH 2016; abstract 343
Phase 1/2 Dose-escalation and Expansion

**Dose Escalation**
- Advanced hematologic malignancies with IDH2 mutation
- Continuous 28 day cycles
- Cumulative daily doses of 50-650 mg

**Expansion Phase 1**
- Any hematologic malignancy ineligible for other arms
- R/R AML age <60, excluding patients relapsed post-BMT
- Untreated AML patients age ≥60 who decline standard of care
- R/R AML age ≥60, or any age if relapsed post-BMT

**Phase 2**
- Accrual Completed
- Enasidenib 100 mg PO QD
- R/R AML (N=108)

**N=239**
- R/R AML: 176
- Untreated AML: 37
- MDS: 17
- Other: 9

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

#### MDS Patients (N=17) n (%)

<table>
<thead>
<tr>
<th>Overall response rate (CR + PR + mCR + HI)</th>
<th>10/17 (59)</th>
</tr>
</thead>
</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
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
<table>
<thead>
<tr>
<th>Reasons for “failure” in azacitidine study</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>9% didn’t tolerate AZA</strong> (69% were not responding, 31% had an initial response)</td>
</tr>
<tr>
<td><strong>55% primary failure</strong> (progression in 60%, stable disease without response in 40%)</td>
</tr>
<tr>
<td><strong>36% secondary failure</strong> after initial response (best response: CR 20%, PR 7%, HI 73%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcomes after failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median overall survival for whole cohort post-AZA: <strong>5.6 months</strong></td>
</tr>
<tr>
<td>2 year survival: <strong>15%</strong></td>
</tr>
<tr>
<td>Favorable factors: female, younger (&lt;60), better risk karyotype, &lt;10% blasts, some response to azacitidine</td>
</tr>
</tbody>
</table>

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


Slide borrowed from Dr. David Steensma
Stem Cell Transplantation
AGE DISTRIBUTION OF PATIENTS WITH MDS

- Patients with MDS
- Patients transplanted for MDS

0% - 10% - 20% - 25%

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

CIBMTR
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).

Conditioning — Donor Cells — Engraftment — Graft-vs.-MDS

Permitted to use from Dr. Bejar
Complications of Transplantation

- GVHD
- Chemotherapy Toxicity
- Infections
- Relapse
The Decision – Whether and When

HIGH RISK MDS STANDARD RISK OF TRAUMPLANT RELATED DEATH

SURVIVAL, %

TIME
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
Allogeneic stem cell transplantation

• Transplant is curative therapy that offers survival advantage when applied at an optimal point

• Age is not itself a contraindication – but comorbidities that accompany age in some people can be
What's new on the Horizon
• 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
Questions?