Myelodysplastic Syndromes: Understanding your diagnosis and current and emerging treatments

Shyamala Navada, M.D., MSCR
Assistant Professor
Icahn School of Medicine at Mount Sinai
Tisch Cancer Institute
Learning Objectives

• Understand etiology of MDS and common symptoms
• How MDS is related to AML, CMML, MPNs (myelofibrosis) and other bone marrow failure disease states
• Standard treatment options for MDS
• Emerging treatments for MDS
Myelodysplastic syndromes

• Hematopoietic stem cell disorder that results in poor cell growth and differentiation

• Features typically include –
  – Abnormal cell maturation
  – Hyperproliferative bone marrow
  – Low blood counts

• 35-40% transform to acute leukemia

• High-risk patients often have complications due to hemorrhage or infection
Myelodysplastic syndromes

• Disease of older patients with median age > 60
• Mechanism of action currently under study
  – Increased risk can occur with
    • Certain chemotherapy agents and radiation
    • Long-term exposure to benzene and other environmental toxins
  – In many cases, etiology is unknown
  – Molecular mutations may help to elucidate the cause in the future
Myelodysplastic Syndromes

- US Incidence ~ 20,000 new cases/annually (2/3 low risk)

- US prevalence ~ 55,000 cases

- Incidence is growing as the population lives longer
MDS: Presentation

• No specific clinical findings distinguish MDS from other causes of pancytopenia

• Laboratory evaluation often prompted by signs or symptoms, including
  – Fatigue (anemia)
  – Infections (neutropenia)
  – Bleeding (thrombocytopenia)

Clinical Overlap / Associations

- MDS = clinical diagnosis manifest by cytopenias

- Many overlapping disorders:
  - Acute Myeloid Leukemia
  - Myeloproliferative Disease
  - Paroxysmal Nocturnal Hemoglobinuria
  - Autoimmune diseases:
    - Aplastic Anemia
    - LGL leukemia
    - Pure Red Cell Aplasia

J Maciejewski, M.D. Taussig Cancer Center/ Cleveland Clinic Foundation
American College of Physicians from Young NS. Ann Intern Med. 2002 Apr 2;136(7):534-46
International Prognostic Scoring System (IPSS)

• Predicts survival and transformation to leukemia for patients with untreated primary MDS
  – Bone marrow blasts
  – Cytogenetics
  – Number of significant cytopenias

Greenberg et al. Blood 1997: 89(6); 2079-2088
# IPSS in MDS

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>0.5</th>
<th>1.0</th>
<th>1.5</th>
<th>2.0</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blasts</strong></td>
<td>&lt;5</td>
<td>5-10</td>
<td>---</td>
<td>11-20</td>
<td>21-30</td>
</tr>
<tr>
<td><strong>Karyotype</strong></td>
<td>Good</td>
<td>Int</td>
<td>Poor</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td><strong>Cytopenias</strong></td>
<td>0/1</td>
<td>2/3</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Karyotype:**
- **Good:** Normal, -Y, del 5q, del 20q
- **Poor:** Complex (>3 abnormalities, abnormal chromosome 7)
- **Intermediate:** All others

Greenberg et al. Blood 1997: 89(6); 2079-2088
## IPSS

<table>
<thead>
<tr>
<th>Risk</th>
<th>Score</th>
<th>Median Survival (years)</th>
<th>Time to 25% AML transformation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>0</td>
<td>5.7</td>
<td>9.4</td>
</tr>
<tr>
<td>Intermediate-1</td>
<td>0.5-1.0</td>
<td>3.5</td>
<td>3.3</td>
</tr>
<tr>
<td>Intermediate-2</td>
<td>1.5-2.0</td>
<td>1.2</td>
<td>1.1</td>
</tr>
<tr>
<td>High</td>
<td>≥2.5</td>
<td>0.4</td>
<td>0.2</td>
</tr>
</tbody>
</table>

Greenberg et al. Blood 1997: 89(6); 2079-2088
Revised IPSS

• Larger database based on 7012 patients
• Novel Components
  – Five cytogenetic prognostic subgroups
  – Splitting the low marrow blast percentage value (0-2% and 2-5%)
  – Evaluation of depth of cytopenias
  – Patient age, performance status, serum ferritin, and LDH are significant for survival but not for AML transformation
New Cytogenetic Classification of MDS

## IPSS-R Prognostic Score Values

<table>
<thead>
<tr>
<th>Prognostic Variable</th>
<th>0</th>
<th>0.5</th>
<th>1</th>
<th>1.5</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytogenetics</td>
<td>Very good</td>
<td>----</td>
<td>Good</td>
<td>----</td>
<td>Intermediate</td>
<td>Poor</td>
<td>Very Poor</td>
</tr>
<tr>
<td>BM Blast %</td>
<td>≤2</td>
<td>----</td>
<td>≥2% - &lt;5%</td>
<td>----</td>
<td>5% - 10%</td>
<td>&gt;10%</td>
<td>----</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>≥10</td>
<td>----</td>
<td>8 - &lt;10</td>
<td>&lt;8</td>
<td>----</td>
<td>----</td>
<td>----</td>
</tr>
<tr>
<td>Platelets</td>
<td>≥100</td>
<td>50 - &lt;100</td>
<td>&lt;50</td>
<td>----</td>
<td>----</td>
<td>----</td>
<td>----</td>
</tr>
<tr>
<td>ANC</td>
<td>≥0.8</td>
<td>&lt;0.8</td>
<td>----</td>
<td>----</td>
<td>----</td>
<td>----</td>
<td>----</td>
</tr>
</tbody>
</table>

Greenberg P, et al. Blood 2012:120(12); 2454-65
Revised IPSS

• Prognostic model with five risk categories
  – Very low \( \leq 1.5 \)
  – Low \( >1.5 - 3 \)
  – Intermediate \( >3-4.5 \)
  – High \( >4.5-6 \)
  – Very High \( >6 \)

Greenberg P, et al. Blood 2012:120(12); 2454-65
IPSS-R Prognostic Risk Based Categories: Survival and Risk of AML Evolution

Greenberg P, et al. Blood 2012:120(12); 2454-65
Survival Based on Patient Age in IPSS-R

Greenberg P, et al. Blood 2012:120(12); 2454-65
Treatment Algorithm

Confirmation of Diagnosis of MDS

Stage

Lower Risk MDS
- GF
- Len
- Aza

Higher-Risk MDS
- AlloSCT
- Aza/HMA
- AML-tx

Clinical trial

AlloSCT

Supportive Therapies

- Red cell transfusions
- Erythropoiesis-stimulating agents
- Myeloid cytokines
- Thrombopoietic growth factors
- Iron chelation therapy
Red cell transfusions

• Anemia is the most common cytopenia in patients with lower-risk MDS
  – Hemoglobin <10
  – Seen in over 50% of newly diagnosed disease
  – Associated with worse performance status and quality of life
  – Transfusion dependence is associated with higher risk of progression to leukemia and higher mortality rate
RBC Transfusion Dependence and Survival

What are Hematopoietic Growth Factors?

• Synthetic versions of proteins normally made in the body to stimulate growth of red cells, white cells and platelets
  – Promote growth and differentiation
  – Inhibitors of cell death

• RED CELL Growth Factors
  – Erythropoietin (EPO, Procrit®, Epogen®)
  – Darbepoietin (Aranesp®)

• WHITE CELL Growth Factors
  – Granulocyte colony stimulating factor (GCSF, Neupogen®)
  – Granulocyte-macrophage colony stim factor (GM-CSF, Leukine®)
  – Peg-filgrastim (Neulasta®)

• PLATELETET Growth Factors
  – Thrombopoietin (TPO, romiplostim, Nplate®)

• Note, these are not FDA-approved for MDS
Erythropoiesis-Stimulating Agents (ESAs)

• Appears to have better efficacy in patients with
  – Lower serum epo levels (<500)
  – Absent or low transfusion requirement (<2 units/month)

• Can be used in combination with G-CSF
Erythropoiesis Stimulating Agents

- Most responses to ESAs occur within 8-12 weeks of treatment
- Avoid increases of Hb > 12 g/dL
- Monitor iron studies during ESA treatment
Problem with Erythropoiesis Stimulating Agents

• Studies of EPO in solid tumor patients showed increased heart attacks, stroke, heart failure, blood clots, increased tumor growth, death, especially when hgb >12

• Has resulted in concern for MDS patients, but NO DATA yet showing these effects in MDS patients

• Has had major effects on insurance coverage
Thrombocytopenia

- Platelet transfusions
- Steroids/Intravenous immunoglobulin
- Danazol
- Thrombopoietic growth factors
  - Currently being tested in clinical trial
Effect of Platelets on Survival and AML Transformation

Thrombopoietin Receptor Agonists

- Eltrombopag/Romiplostim
- Clinical evidence of activity in Phase II studies with multilineage responses (platelets, erythrocytes, neutrophils)
- Responses seen across all IPSS risk groups
- Increase in circulating blasts has been reported
- Ongoing trials and long-term follow-up are needed
Stimulating White Blood Cells and Platelets

• **White Cell Growth Factors:**
  • Not routine – Don’t treat the number, treat the patient
    • active infections - recurrent/resistant infections
    • neutropenic fever
  • Can be combined with red cell growth factors to improve responses in some patients
  • Side effects: fever, bone pain, injection site reactions
    • Does stimulating white blood cells cause leukemia?

• **Platelet Growth Factors:**
  • Not routine – Don’t treat number, treat the patient
    • Bleeding history - Single digit platelets
  • Romiplostim: Azacitidine Rx pts Romiplostim vs placebo
    • Less bleeding events
    • Does stimulating platelets cause leukemia?
Should transfusion dependent MDS patients receive iron chelation therapy?
## Role of Iron Chelation in MDS: Controversy

### Pros

- *Retrospective* data: ferritin >1000 associated with worse OS in RA/RARS (*Malcovati et al JCO*)
- MDS transplant outcomes dependent on baseline ferritin (*Armand et al Blood*)
- Convincing benefit from chelation in thalassemia major
- Other speculative benefits in MDS: reduce infection, improve hematopoiesis
- Orally bioavailable agent
- Can measure iron deposition easily with T2* MRI

### Cons

- OS of MDS patients shorter than children with thalassemia
- Chelation process slow
- MRI failed to show cardiac iron loading in most heavily transfused MDS patients
- Ferritin unreliable marker of iron burden
- Iron-related event rate in MDS low
- Retrospective data subject to bias
- No prospective data showing benefit from chelation in MDS
- Chelation is expensive, inconvenient
- Oral chelation associated with GI toxicity and other AE (e.g. renal injury, infection, auditory/ocular AEs)
Iron Chelation Therapy

- Iron overload can lead to organ damage, particularly cardiac dysfunction
  - Consider iron chelation for lower-risk patients who have received more than 20-30 lifetime units of red cells, or if ferritin $>2500$
  - Consider chelation for patients who are candidates for stem cell transplants
Immunosuppressive Therapies

• ATG +/- cyclosporine

• Factors predicting response
  – Younger age (<60 years)
  – Low IPSS score
  – Short duration of transfusion dependence
  – Presence of HLA-DR15 phenotype
Immunomodulatory Drugs

• Lenalidomide
  – Reduces red cell transfusion dependence and improves erythropoiesis in patients with lower-risk MDS with del (5q)
  – More likely to respond if low transfusion requirements, high platelet counts, normal LDH, shorter duration of disease
  – Hematologic toxicity is frequent adverse effect
<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>patients</th>
<th>Overall response</th>
<th>Transfusion-independence (TI)</th>
<th>Time to response</th>
<th>Hb increase</th>
<th>Cytogenetic response (complete)</th>
<th>Median TI duration</th>
<th>Grade 3-4 Neutro-thrombocytopenia</th>
</tr>
</thead>
<tbody>
<tr>
<td>del(5q) Low/Int-1 MDS-003</td>
<td>148</td>
<td>76%</td>
<td>67%</td>
<td>4.6 wks</td>
<td>5.4 g/dl</td>
<td>73%* (45%)</td>
<td>Not reached FU 2 yrs</td>
<td>55-44%</td>
<td></td>
</tr>
<tr>
<td>del(5q) Low/Int-1 ATU</td>
<td>95</td>
<td>65%</td>
<td>63%</td>
<td>16 wks (TI)</td>
<td>ND</td>
<td>40% (20%)</td>
<td>Not reached FU 16 mo</td>
<td>62-25%</td>
<td></td>
</tr>
<tr>
<td>del(5q) Low/Int-1 MDS-004</td>
<td>69 (5 mg/d)</td>
<td>ND</td>
<td>50%</td>
<td>3.3 wks</td>
<td>5.1</td>
<td>17% (11%)</td>
<td>Not reached 106 wks</td>
<td>74-33% 75-41%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>69 (10 mg/d)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>del(5q) Int-2/High risk</td>
<td>47</td>
<td>27%</td>
<td>25%</td>
<td>2-4 cycles</td>
<td>ND</td>
<td>19% (10%)</td>
<td>25 wks</td>
<td>76-79%</td>
<td></td>
</tr>
<tr>
<td>Non del(5q) MDS-002</td>
<td>215</td>
<td>43%</td>
<td>26%</td>
<td>4.8 wks</td>
<td>3.2 g/dl</td>
<td>20% (9%)</td>
<td>41 wks</td>
<td>30-25%</td>
<td></td>
</tr>
</tbody>
</table>
Methyltransferase Inhibitor Induced DNA Hypomethylation and Gene Activation

Navada et al. JCI 2014: 124(1); 40-46
Hypomethylating Agents

• Azacitidine (Aza C) affects DNA methylation and gene expression
• Phase III trial comparing Aza C to best supportive care
  – Significantly higher response rates
  – Delay in transformation to acute myeloid leukemia or death
  – Improved quality of life
  – Improved survival
CALBG 9221: azacitidine vs supportive care – summary of quality of life findings

<table>
<thead>
<tr>
<th>EORTC QoL Scale</th>
<th>Azacitidine vs supportive care (n = 191), p value</th>
<th>Crossover subset (n = 38), p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical functioning</td>
<td>0.002</td>
<td>0.0040</td>
</tr>
<tr>
<td>Fatigue</td>
<td>0.010</td>
<td>0.0001</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>0.0014</td>
<td>0.0002</td>
</tr>
<tr>
<td>Insomnia</td>
<td>0.35</td>
<td>0.25</td>
</tr>
<tr>
<td>Social functioning</td>
<td>0.41</td>
<td>0.156</td>
</tr>
<tr>
<td>Overall QoL</td>
<td>&lt; 0.0001</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

EORTC = European Organisation for Research and Treatment of Cancer; QoL = quality of life.

Significant improvements in physical functioning, fatigue, and dyspnea after crossover to azacitidine

Azacitidine Survival Study - 001

Screening/Central Pathology Review

Investigator CCR Tx Selection

Randomization

CCR

- Best Supportive Care (BSC) only
- Low Dose Ara-C (LDAC, 20 mg/m²/d x 14 d q28-42 d)
- Std Chemo (7 + 3)

BSC was included with each arm
Tx continued until unacceptable toxicity or AML transformation or disease progression

Fenaux et al. Lancet Oncol 2009: 10(3); 223-32
**Overall Survival: Azacitidine vs CCR**

**ITT Population**

Log-Rank p=0.0001

HR = 0.58 [95% CI: 0.43, 0.77]

Deaths: AZA = 82, CCR = 113

**Difference: 9.4 months**

**Fenaux et al. Lancet Oncol 2009: 10(3); 223-32**
Secondary Endpoints – Aza 001

• Time to AML or death
  – 13 mos with AZA vs 7.6 mos with CCR, \( p=0.003 \)

• Time to AML
  – 26.1 mos with AZA vs 12.4 with CCR, \( p=0.004 \)

• RBC Transfusion Independence
  – 45% with AZA vs 11% with CCR, \( p<0.0001 \)

• Infections Requiring IV Antimicrobials
  – Reduced by 33% with AZA vs CCR

Phase III Trial of Decitabine in MDS

Multi-center study in the US and Canada

Open-label with 1:1 randomization between:

Decitabine vs Supportive Care (antibiotics, GF, transfusions)

Eligible Patients (N = 170)

Stratification
IPSS Classification
Prior Chemotherapy
Study Center

Decitabine + Supportive Care (N = 89)

Supportive Care (N = 81)

Kantarjian et al. Cancer 2006;106:1794
## Phase III: Decitabine in MDS: Response

<table>
<thead>
<tr>
<th></th>
<th>Decitabine (n=89)</th>
<th>Supportive Care (n=81)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical Response</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall response (CR + PR)</td>
<td>15 (17%)</td>
<td>0</td>
</tr>
<tr>
<td>CR</td>
<td>8 (9%)</td>
<td>0</td>
</tr>
<tr>
<td>PR</td>
<td>7 (8%)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Clinical Improvement</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall improvement (CR + PR + HI)</td>
<td>27 (30%)</td>
<td>6 (7%)</td>
</tr>
<tr>
<td>HI</td>
<td>12 (13%)</td>
<td>6 (7%)</td>
</tr>
<tr>
<td>Major HI</td>
<td>12 (13%)</td>
<td>5 (6%)</td>
</tr>
<tr>
<td>Minor HI</td>
<td>0 (0%)</td>
<td>1 (1%)</td>
</tr>
</tbody>
</table>

Kantarjian et al. *Cancer* 2006;106:1794
Decitabine vs. Supportive Care
Time to AML or Death All Patients (N=170)

Kantarjian et al. *Cancer*. 2006

![Graph showing survival rates](image)
# Summary of Phase III Trials Using Hypomethylating Agents in MDS

<table>
<thead>
<tr>
<th>Trial</th>
<th>Drug</th>
<th>Number of patients</th>
<th>Dose/Duration of Administration</th>
<th>Route of Administration</th>
<th>Response Rate (% CR/PR/HI)</th>
<th>Time to AML or Death (months)</th>
<th>Median Survival (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CALGB 9221</td>
<td>AzaC</td>
<td>99</td>
<td>75 mg/m²/d x 7 days</td>
<td>SC</td>
<td>60%(7/16/37)</td>
<td>21</td>
<td>20</td>
</tr>
<tr>
<td>BSC</td>
<td></td>
<td>92</td>
<td></td>
<td></td>
<td>5%</td>
<td>12</td>
<td>14</td>
</tr>
<tr>
<td>AZA-001</td>
<td>AzaC</td>
<td>179</td>
<td>75 mg/m²/d x 7 days</td>
<td>SC</td>
<td>51%(17/12/22)</td>
<td>17.8</td>
<td>24.5</td>
</tr>
<tr>
<td>BSC/Chem</td>
<td></td>
<td>179</td>
<td></td>
<td></td>
<td>29%</td>
<td>11.5</td>
<td>15</td>
</tr>
<tr>
<td>D-0007</td>
<td>DAC</td>
<td>89</td>
<td>Q8 hours X 3 days</td>
<td>IV</td>
<td>30%(9/8/13)</td>
<td>12.1</td>
<td>14</td>
</tr>
<tr>
<td>BSC</td>
<td></td>
<td>81</td>
<td></td>
<td></td>
<td>7% (0/0/7)</td>
<td>7.8</td>
<td>14.9</td>
</tr>
<tr>
<td>EORTC-06011</td>
<td>DAC</td>
<td>119</td>
<td>Q8 hours X 3 days</td>
<td>IV</td>
<td>34%(13/6/15)</td>
<td>8.8</td>
<td>10.1</td>
</tr>
<tr>
<td>BSC</td>
<td></td>
<td>114</td>
<td></td>
<td></td>
<td>2% (0/0/2)</td>
<td>6.1</td>
<td>8.5</td>
</tr>
</tbody>
</table>

Navada et al. JCI 2014: 124(1); 40-46
Common Side Effects of Hypomethylating Agents

• Nausea/Gastrointestinal side-effects
  – Premedicate with Zofran
  – Monitor for constipation

• Myelosuppression
  – More common in initial cycles
  – Often need 4-6 cycles to see response

• Discomfort at Injection Site (Azacitidine)

• Discuss any possible side-effects with your doctor
Outcome of Patients Treated for Myelodysplastic Syndromes and Secondary AML After Azacitidine Failure

At a median follow-up of 15 months after azacitidine failure, the median OS of patients with MDS or secondary AML (sAML) was 6 months.

![Graph showing overall survival over days after AZA failure]

<table>
<thead>
<tr>
<th>Type of salvage</th>
<th>N=</th>
<th>Response rate*</th>
<th>Median OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unknown (UNK)</td>
<td>215</td>
<td>NA</td>
<td>3.6 months</td>
</tr>
<tr>
<td>Palliative care (PC)</td>
<td>160</td>
<td>NA</td>
<td>3.3 months</td>
</tr>
<tr>
<td>Cytotoxic therapy (CT)</td>
<td>84</td>
<td>1/25 and 5/33**</td>
<td>7.6 months</td>
</tr>
<tr>
<td>Investigational therapy (IT)</td>
<td>56</td>
<td>4/39</td>
<td>13.2 months</td>
</tr>
<tr>
<td>Allogeneic Transplantation (ASCT)</td>
<td>50</td>
<td>17/25</td>
<td>18.3 months</td>
</tr>
</tbody>
</table>

Allogeneic Stem Cell Transplant

• Only curative therapy for MDS
• Many patients are not candidates because of age, comorbidities, or lack of suitable donor
• For patients with low and int-1 IPSS risk, better outcomes when transplant is delayed until disease progression (but before development of AML)
Allogeneic SCT for MDS: General Principles and the Decision

SCT is potentially curative:
- however part of the benefit is lost due to its morbidity + mortality

Low risk pts:
- risk of SCT > risk of disease

High risk pts:
- risk of disease > risk of SCT

Borrowed from Cutler, C et al
Hypomethylating Failures

- Azacitidine and vorinostat
- Azacitidine and lenalidomide
- Oral azacitidine
- PDL-1 inhibitors
- Rigosertib
- Azacitidine and rigosertib
Genes Recurrently Mutated in MDS

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

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

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

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

Others
- TP53
- NPM1
- NOTCH?
- MAML?
- ZSWIM4?
- UMODL1?

Others
- BCOR

Bejar R.
Gene Mutations and Survival

- **TET2 (349^{wt} vs. 90^{mut})**: $p$-value = 0.48
- **ASXL1 (376^{wt} vs. 63^{mut})**: $p$-value = 0.003
- **RUNX1 (401^{wt} vs. 38^{mut})**: $p$-value < 0.001
- **TP53 (406^{wt} vs. 33^{mut})**: $p$-value < 0.001
- **EZH2 (411^{wt} vs. 28^{mut})**: $p$-value < 0.001
- **NRAS (423^{wt} vs. 16^{mut})**: $p$-value = 0.006

ACE-011 (Sotatercept) and ACE-536 Novel Ligand Traps for TGFβ Superfamily Ligands

<table>
<thead>
<tr>
<th>Fusion protein with ligand trap activity toward the activin type 2 receptors</th>
<th>Drug does not bind EPO receptors</th>
<th>Heme effect</th>
<th>Bone effect</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ACE-011 (Sotatercept)</strong></td>
<td>Extracellular Domain of ActRIIA</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Fc Domain of human IgG₁ Antibody</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ACE-536</strong></td>
<td>Modified Extracellular Domain of ActRIIB</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Fc Domain of human IgG₁ Antibody</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Luspatercept in MDS: Background

- **TGF-β Superfamily Ligands:** GDF11, etc.

- **Luspatercept**
  - Fusion protein containing modified activin receptor type IIB (ActRIIB)
  - Activin Receptor Domain
  - Human IgG Fc Domain

- **Mechanism is distinct from erythropoietin**
- **Acts on late-stage erythropoiesis to increase mature RBCs in the circulation**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Disease Type</th>
<th>No</th>
<th>Dose (mg/m²) Schedule</th>
<th>CR</th>
<th>ORR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gore</td>
<td>MDS/AML</td>
<td>36</td>
<td>azacitidine/phenylbutyrate</td>
<td>14%</td>
<td>38%</td>
</tr>
<tr>
<td>Prebet/Gore</td>
<td>MDS/AML</td>
<td>136</td>
<td>azacitidine/entinostat</td>
<td>12%</td>
<td>44%</td>
</tr>
<tr>
<td>Soriano</td>
<td>MDS/AML</td>
<td>53</td>
<td>azaC/VPA/ATRA</td>
<td>22%</td>
<td>42%</td>
</tr>
<tr>
<td>Garcia-Manero</td>
<td>MDS/AML</td>
<td>37</td>
<td>azacitidine/MGCD0103</td>
<td>11%</td>
<td>52%</td>
</tr>
<tr>
<td>Silverman</td>
<td>MDS/AML</td>
<td>23</td>
<td>azacitidine/vorinostat</td>
<td>48%</td>
<td>87%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>61%CRi</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Garcia-Manero</td>
<td>AML/MDS</td>
<td>54</td>
<td>decitabine/VPA</td>
<td>19%</td>
<td>22%</td>
</tr>
<tr>
<td></td>
<td>AML</td>
<td>10</td>
<td></td>
<td>40%</td>
<td>50%</td>
</tr>
<tr>
<td>Kirschbaum</td>
<td>MDS/AML</td>
<td>60</td>
<td>decitabine/Vorinostat</td>
<td>22%</td>
<td>45%</td>
</tr>
<tr>
<td>Blum</td>
<td>AML</td>
<td>25</td>
<td>decitabine/VPA</td>
<td>16%</td>
<td>44%</td>
</tr>
<tr>
<td>Issa</td>
<td>MDS/AML</td>
<td>31</td>
<td>decitabine/vorinostat</td>
<td>3%</td>
<td>17%</td>
</tr>
<tr>
<td>Yee</td>
<td>MDS/AML</td>
<td>27</td>
<td>decitabine/vorinostat</td>
<td>4%</td>
<td>16%</td>
</tr>
</tbody>
</table>

Navada et al. JCI 2014: 124(1); 40-46
Acute Myeloid Leukemia

• Recent FDA approved therapies
  – Midostaurin (FLT3+ disease)
  – Enasidenib (IDH2+ disease)
  – Gemtuzumab ozogamicin (CD 33+ disease)
  – Vyxeos (AML from MDS or therapy-related disease)
Future Strategies

• Combinations – Activity with reduced toxicity and improved tolerability and deliverability
• Surrogate intermediate clinical endpoint to enhance drug development
• Biomarkers to select target populations and enhance treatment effects and outcome
• Education
  • Patient Selection
  • Duration
  • Optimization of Care
Conclusions: Optimizing Therapy

- Effective treatments for MDS exist
  - IPSS – starting point for risk stratification
  - Important to set goals of therapy
- Growth Factors, support
- Lenalidomide = lower risk, goal ↓ transfusions
- DNA methyltransferase inhibitors = high risk
  - Azacitidine associated with improved survival
- Allogeneic stem cell transplant can be curative but not for all patients
- New biology, new targets, new drugs coming