Myelodysplastic syndrome

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MDS

- Clonal hematopoietic disorder - multilineage hematopoietic progenitor
- Ineffective hematopoiesis
- Dysplasia
- Peripheral cytopenias and bone marrow failure
- Risk of transformation to AML in 35 to 40%

RBC – Carries oxygen in blood
WBC – Fights against infection
Platelets – prevents bleeding
How common is MDS?

Zeidan AM et al. Blood Rev 2019
How does it start?

- Series of genetic events over time
- Exposure to environmental factors
- Genetic predisposition
- Prior chemotherapy or radiotherapy
- Epigenetic abnormalities
- Abnormal DNA repair
- Decreased cell death (apoptosis)
- Telomerase dysfunction
- Overlaps with other disorders such as aplastic anemia, paroxysmal nocturnal hemoglobinuria

Issa J. Blood 2013
Young NS. Ann Intern Med. 2002
Symptoms and signs

- Asymptomatic
- Fatigue
- Easy bleeding
- Recurrent infections
- Fever
- Night sweats

Anemia
- Tiredness
- Fatigue
- Shortness of breath

Leukopenia
- Increased risk of infections

Thrombocytopenia
- Increased bleeding
DIAGNOSIS

- History and physical exam – symptoms, medications, transfusions

- Peripheral blood counts and smear review

- Bone marrow biopsy and aspiration
  - Bone marrow blasts %
  - Cytogenetics/FISH
  - Iron stain
  - Reticulin stain

Cytogenetics

FISH
<table>
<thead>
<tr>
<th>MDS criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cytopenia +</strong></td>
</tr>
<tr>
<td><strong>&gt;10% dysplastic cells in 1 or more lineages, or</strong></td>
</tr>
<tr>
<td><strong>5-19% blasts, or</strong></td>
</tr>
<tr>
<td><strong>MDS chromosomal abnormality or</strong></td>
</tr>
<tr>
<td><strong>Specific MDS mutation</strong></td>
</tr>
<tr>
<td>Conditions that mimic MDS</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>Vitamin B12/folate deficiency</td>
</tr>
<tr>
<td>HIV /viral infection</td>
</tr>
<tr>
<td>Copper deficiency</td>
</tr>
<tr>
<td>Alcohol abuse</td>
</tr>
<tr>
<td>Medications (methotrexate, azathioprine, recent chemotherapy)</td>
</tr>
<tr>
<td>Congenital syndromes (Fanconi anemia)</td>
</tr>
<tr>
<td>Autoimmune conditions (SLE, ITP)</td>
</tr>
</tbody>
</table>
How is MDS treated?
Principles of MDS management

- Risk stratification
- Establishing treatment goals
- Disease specific agents
- Supportive measures
- Allogeneic stem cell transplantation
RISK STRATIFICATION

- IPSS
- R-IPSS
- WPSS
- Low risk IPSS
- Approaches to include genomic features
# IPSS - International prognostic scoring system

<table>
<thead>
<tr>
<th>Survival and AML Evolution</th>
<th>Score Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prognostic variable</td>
<td>0</td>
</tr>
<tr>
<td>Marrow blasts (%)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>&lt;5</td>
</tr>
<tr>
<td>Karyotype&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Good</td>
</tr>
<tr>
<td>Cytopenia&lt;sup&gt;d&lt;/sup&gt;</td>
<td>0/1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>IPSS Risk category (% IPSS pop.)</th>
<th>Overall score</th>
<th>Median survival (y) in the absence of therapy</th>
<th>25% AML progression (y) in the absence of therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>LOW (33)</td>
<td>0</td>
<td>5.7</td>
<td>9.4</td>
</tr>
<tr>
<td>INT-1 (38)</td>
<td>0.5-1.0</td>
<td>3.5</td>
<td>3.3</td>
</tr>
<tr>
<td>INT-2 (22)</td>
<td>1.5-2.0</td>
<td>1.1</td>
<td>1.1</td>
</tr>
<tr>
<td>HIGH (7)</td>
<td>≥2.5</td>
<td>0.4</td>
<td>0.2</td>
</tr>
</tbody>
</table>

![IPSS Classification: Survival graph](image1)

![IPSS Classification: AML Transformation graph](image2)

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### Revised IPSS

<table>
<thead>
<tr>
<th>Prognostic variable</th>
<th>Score Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.5</td>
</tr>
<tr>
<td>Cytogenetic&lt;sup&gt;e&lt;/sup&gt;</td>
<td>Very good</td>
</tr>
<tr>
<td>Marrow blasts (%)</td>
<td>≤2</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>≥10</td>
</tr>
<tr>
<td>Platelets</td>
<td>≥100</td>
</tr>
<tr>
<td>ANC</td>
<td>≥0.8</td>
</tr>
</tbody>
</table>

### IPSS-R Risk category (% IPSS-R pop.)

<table>
<thead>
<tr>
<th>Overall score</th>
<th>Median survival (y) in the absence of therapy</th>
<th>25% AML progression (y) in the absence of therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>VERY LOW (19)</td>
<td>≤1.5</td>
<td>8.8</td>
</tr>
<tr>
<td>LOW (38)</td>
<td>&gt;1.5-≤3.0</td>
<td>5.3</td>
</tr>
<tr>
<td>INT&lt;sup&gt;3&lt;/sup&gt; (20)</td>
<td>&gt;3.0-≤4.5</td>
<td>3</td>
</tr>
<tr>
<td>HIGH (13)</td>
<td>&gt;4.5-≤6.0</td>
<td>1.6</td>
</tr>
<tr>
<td>VERY HIGH (10)</td>
<td>&gt;6.0</td>
<td>0.8</td>
</tr>
</tbody>
</table>

NCCN guidelines MDS 2019
Low risk:
IPSS low, intermediate-1
Revised IPSS – very low, low, intermediate
Survival – 3-8 years without therapy
Focus to improve marrow function, minimize complications and improve QOL

High risk
IPSS intermediate-2, high
Revised IPSS – high, very high
Survival - <2 years without therapy, high risk of AML transformation
Focus to eradicate the disease, reduce AML transformation, improve survival and QOL

 Therapy related
Aggressive subtype with poor response to therapy
 Usually considered for allogeneic stem cell transplantation
Low risk disease

- Observation
- Del5q – Lenalidomide
- Serum EPO ≤500 with anemia – Erythropoietin or darbepoetin/G-CSF
- Immunosuppressive therapy – ATG/cyclosporine

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Lenalidomide

- Immunomodulatory agent shown to have activity in patients with del5q MDS (and some patients without del5q)
- Dose: 10mg once daily, oral

Table 2. Erythroid Response to Lenalidomide.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Continuous Daily Dosing (N=102)</th>
<th>21-Day Dosing (N=46)</th>
<th>All Patients (N=148)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transfusion independence</td>
<td>71 (70)</td>
<td>28 (61)</td>
<td>99 (67)</td>
</tr>
<tr>
<td>95% CI</td>
<td></td>
<td></td>
<td>59–74</td>
</tr>
<tr>
<td>≥50% decrease in no. of transfusions</td>
<td>8 (8)</td>
<td>5 (11)</td>
<td>13 (9)</td>
</tr>
<tr>
<td>95% CI</td>
<td></td>
<td></td>
<td>5–15</td>
</tr>
<tr>
<td>Total transfusion response</td>
<td>79 (77)</td>
<td>33 (72)</td>
<td>112 (76)</td>
</tr>
<tr>
<td>95% CI</td>
<td></td>
<td></td>
<td>68–82</td>
</tr>
<tr>
<td>Time to response — wk</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>4.7</td>
<td>4.3</td>
<td>4.6</td>
</tr>
<tr>
<td>Range</td>
<td>1–34</td>
<td>1–49</td>
<td>1–49</td>
</tr>
</tbody>
</table>

Table 4. Grade 3 and 4 Treatment-Related Adverse Events.

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>20 (20)</td>
<td>8 (17)</td>
<td>45 (44)</td>
<td>8 (17)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>37 (36)</td>
<td>14 (30)</td>
<td>7 (7)</td>
<td>7 (15)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia (not otherwise specified)</td>
<td>4 (4)</td>
<td>2 (4)</td>
<td>4 (4)</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukopenia (not otherwise specified)</td>
<td>3 (3)</td>
<td>2 (4)</td>
<td>4 (4)</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>5 (5)</td>
<td>4 (9)</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>2 (2)</td>
<td>1 (2)</td>
<td>2 (2)</td>
<td>1 (2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pruritus</td>
<td>2 (2)</td>
<td>2 (4)</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>2 (2)</td>
<td>2 (4)</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muscle cramp</td>
<td>3 (3)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>1 (1)</td>
<td>2 (4)</td>
<td>1 (1)</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>3 (3)</td>
<td>1 (2)</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4 (4)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deep-vein thrombosis</td>
<td>3 (3)</td>
<td>1 (2)</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>1 (1)</td>
<td>2 (4)</td>
<td>1 (1)</td>
<td>1 (2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>1 (1)</td>
<td>1 (2)</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>1 (1)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
ESA/G-CSF

- Erythropoietin-alfa or Darbepoetin
- Low risk MDS with anemia
- Given as subcutaneous injection
- Can be given with or without G-CSF
- Response rate 40-60%
- Target Hb of 10-12

Immunosuppressive therapy

ATG, cyclosporine

- Hypoplastic bone marrow
- Normal cytogenetics
- Low risk disease
- PNH clones
- HLA-DR15
- Young (age <60)

Stahl M et al. Blood Adv 2018
Transfusions and iron chelation

- RBC transfusion for anemia and platelet transfusion for thrombocytopenia
- Higher RBC transfusion burden increases the risk of complications from iron overload
- Iron chelation: Deferoxamine or deferasirox
- Patients who have received or are anticipated to receive greater than 20 RBC transfusions
- Patients for whom ongoing RBC transfusions are anticipated
- Patients with serum ferritin levels greater than 2500 ng/mL

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High risk disease

- Hypomethylating agents – Decitabine or Azacitidine
- Allogeneic stem cell transplantation

NCCN guidelines MDS 2019
Azacitidine

- Hypomethylating agents
- Given SC or IV, typically 7 days
- Usually takes up to 6 cycles to see response
- Alternative dosing schedules have been studied

OS benefit: 9.4 mon
Time to AML: 17.8 vs. 11.5 mos
TI: 45% vs. 11%
ORR 50%, CR 17%

Feneaux et al. Lancet Oncol 2009
Decitabine

- Hypomethylating agent
- Given as IV – typically 20mg/m2 for 5 days
- Can take 4 cycles to have response
- Median time to AML - 4.3 months greater
- 17% CR+PR

Kantarjian et al. Cancer 2006
Allogeneic stem cell transplant

• Curative option

• Often limited by factors such as patient fitness, comorbid conditions and availability of donor

• Cures MDS in about 30-40% of patients

• Risk of death from transplant is 15-20%

• Risk of relapse 35-50%

Infections  
GVHD  
Disease relapse
Unmet need...

- Disease progression after decitabine or azacitidine
- Disease progression after lenalidomide
- Disease relapse after allogeneic stem cell transplantation
POTENTIAL NEW AGENTS

Aleshin et al. Blood Adv 2018
Luspatarcept

First-in-class erythroid maturation agent

- Recent clinical trial showed significant benefit in terms of RBC transfusion independence
- 37.9% achieved RBC-TI for ≥ 8 weeks
- Low risk disease
- Not FDA approved yet

List A et al. ASH 2018
Few trials...

Allo vs Hypomethylating/Best Supportive Care in MDS (BMT CTN 1102)

Hypomethylating Properties of Freeze-dried Black Raspberries (BRB) in Patients With Myelodysplastic Syndrome or Myelodysplastic Syndrome/Myeloproliferative Neoplasm

A Trial to Evaluate the Potential Impact of Renal Impairment on the Pharmacokinetics and Safety of CPX-351

Safety Study of MGD006 in Relapsed/Refractory Acute Myeloid Leukemia (AML) or Intermediate-2/High Risk MDS
QUESTIONS?