Myelodysplastic Syndromes

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Primary Objectives

• To review clinical presentation of MDS and differential diagnosis
• To review the epidemiology and diagnostic evaluation of patients with MDS
• To review insights into the pathogenesis of MDS
• To review treatment recommendations for patients with low and high risk MDS
• To discuss special cases: hypoplastic MDS, MDS with 5q deletion, MDS with Ringed Sideroblasts, ICUS/CHIP

Case

• 71 year old female with fatigue and neuropathy is referred to OSU for second opinion and concern for a marrow disorder.

• WBC 1.8 (10% segs), Hg 8.3g/dL, Plt 277
  • Bone marrow biopsy with dyserythropoiesis and dysmegakaryopoiesis, low blasts
  • Normal female karyotype

Case continued

• Exam findings:
  • Dentures in place
  • Severe sensory and motor neuropathy
Case continued

- Exam findings:
  - Dentures in place
  - Severe sensory and motor neuropathy

- She mentioned that she had recently seen on ABC news a report of Zinc toxicity from Poligrip.
  - She stopped using the product about a month prior, but had used it for 4-5 years.

Case continued

- Her Zinc level was high at 2800ug/L in the urine with Zn/Cr ratio of 5456/ug/g creat (nl 100-900)

- Serum copper level is undetectable

Differential Diagnosis: Non-Hematologic Causes of Cytopenia

- Reactive/Temporary Cause
  - Drug Effects
  - Infection (viral, bacterial, etc.)

- Nutritional Deficiencies
  - B12, folate, copper, iron
  - Alcoholism, liver dysfunction

- Autoimmune Disorders
  - Hypothyroidism
  - Rheumatologic Disorders

- Copper replacement given, CBC normal within 3 weeks.
Case 2

- 63-year-old woman with no PMH presents to her internist for her first evaluation in 5 years to re-establish care.
  - She reported worsening fatigue worsening for about a year
  - Mild shortness of breath with activity
  - Occasional bruising but usually after an injury
  - Exam: Notable for pallor, mild systolic murmur, and scattered small bruises

Laboratory Results:

<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hgb</td>
<td>9.2g/dL</td>
</tr>
<tr>
<td>MCV</td>
<td>101</td>
</tr>
<tr>
<td>WBC</td>
<td>2.3</td>
</tr>
<tr>
<td>ANC</td>
<td>690/uL</td>
</tr>
<tr>
<td>Blasts</td>
<td>None</td>
</tr>
<tr>
<td>Platelet</td>
<td>64,000/uL</td>
</tr>
<tr>
<td>B12</td>
<td>810</td>
</tr>
<tr>
<td>Folate</td>
<td>20</td>
</tr>
<tr>
<td>Erythropoietin</td>
<td>254 (normal 2-20)</td>
</tr>
</tbody>
</table>

Diagnostic Work-Up

- Peripheral blood smear
- B12, folate, iron studies, copper level
- LDH, haptoglobin, DAT, retic count, epo level
- TSH
- HIV, Hepatitis B and C, and Parvovirus B19
- SPEP, PNH
- If symptomatic, possibly CT abdomen or ultrasound spleen
- Bone marrow biopsy including cytogenetics
- Hematologic neoplasm sequencing panel
**Peripheral Smear**

![Peripheral Smear Image](https://en.wikipedia.org/wiki/Myelodysplastic_syndrome#/media/File:Hypogranular_neutrophil_with_a_pseudo-Pelger-Huet_nucleus_in_MDS.jpg)

**Imaging**

![Imaging Image](https://upload.wikimedia.org/wikipedia/commons/8/89/Tumor_Myelodysplastic_Spleen.JPG)

**Case continued**

- Bone marrow biopsy returns consistent with MDS with 8% blasts.
- Cytogenetics show a complex karyotype with trisomy 8, deletion 7, and deletion of 20q
- Sequencing panel reveals mutations of ASXL1 and TET2

**Epidemiology**

- SEER officially began to track in 2001
  - 15,000 new diagnoses per year
  - Median age at presentation is 70
  - Incidence increases with age
    - < 40 years 0.14 per 100,000
    - ≥ 80 years 36 per 100,000
  - Male predominance
Epidemiology

- Risk factors
  - Age
  - Prior chemotherapy
    - Alkylating agent
      » 5-10 years – chromosome 5 and 7 abnormalities
    - Topoisomerase II inhibitors
      » 1-2 years – 11q23 abnormalities
    - XRT (5-10 years)
  - Benzene exposure (organic solvents)
  - Smokers exposed to environmental agents (OR: 1.45)

Prognostication

International Prognostic Scoring System (IPSS)

- Multivariate analysis of hematologic characteristics of 816 patients at diagnosis
- Also included patients with 20-30% blasts
- Identified 3 variables
  - % of bone marrow blasts
    » <5%; 5-10%; 11-20%, 21-29%
  - Cytogenetic abnormalities
    » Good: Normal, -Y, del(5q), del(20q)
    » Poor: Complex (≥3 abnormalities); abnormal Chr 7
    » Intermediate: All others
  - Number of cytopenias
    » ANC < 1800; Hemoglobin < 10; Platelets < 100,000

IPSS Scores and Associated Risk Groups

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Score</th>
<th>Median Survival (years)</th>
<th>Median Time to AML evolution (years)</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 P Blood 1997; 89: 29:2079
Limitations of the IPSS

- Does not consider severity of cytopenias, just their presence
- Cytogenetic abnormalities were limited and not all patients are represented
- Not designed to use at later time points after diagnosis
- Excluded patients with secondary MDS, therapy-related MDS, and CMML
- Variability in outcomes of patients with lower risk disease

Revised International Prognostic Scoring System (IPSS-R)

- Cytogenetics (added 2 additional groups)
  - Very good: -Y or del(11q)
  - Good: CN, del(5q), del(12p), del(20q) or double abnormality including del(5q)
  - Intermediate: del(7q), +8,+19, i(17q) and any other single or double independent clones
  - Poor: -7, inv(3)(t)(3q)/del(3q), double abnormalities including =7/del(7q) or 3 abnormalities
  - Very Poor: complex (≥3 abnormalities)
- Blast %
  - <2%, 2-5%, 5-10%, >10%
- Cytopenias
  - ANC, hemoglobin, and platelet count all now contribute to the score based on their severity

Revised International Prognostic Scoring System (IPSS-R)

<table>
<thead>
<tr>
<th></th>
<th>Very Low</th>
<th>Low</th>
<th>Intermediate</th>
<th>High</th>
<th>Very high</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Survival (years)</td>
<td>8.8</td>
<td>5.3</td>
<td>3.0</td>
<td>1.6</td>
<td>0.8</td>
</tr>
<tr>
<td>Median time to 25% AML transformation (years)</td>
<td>NR</td>
<td>10.8</td>
<td>3.2</td>
<td>1.4</td>
<td>0.73</td>
</tr>
</tbody>
</table>

Case 2 continued

- IPSS score
  - Intermediate-2 risk group
  - Median survival of 1.2 years
- R-IPSS score
  - Very high risk group
  - Median survival of 0.8 years
Summary of Work-Up

- When to suspect?
  - Unexplained cytopenia
  - Symptoms may include fatigue, SOB, and bleeding or bruising depending on the cell lines involved
- Initial steps in diagnosis?
  - Comprehensive lab studies
  - Consider abdominal imaging if hepatosplenomegaly suspected
- When to refer to hematology?
  - New cytopenia and/or work-up has not shown source of cytopenia
  - If bone marrow biopsy felt to be indicated

Myelodysplastic Syndromes

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Pathogenesis and Treatment

MDS Overlaps with Other Entities

- MDS clinical and histopathological characteristics can overlap with many other hematological disorders
- An accurate diagnosis relies on expertise in interpreting diagnostic tests
Myelodysplastic Syndromes

- Heterogenous group of malignant hematopoietic stem cell disorders
- Characterized by clonal hematopoiesis
- Quantitatively and qualitatively abnormal myeloid differentiation
  - Chronic cytopenias
- Immune dysregulation
- Variable progression to AML

2016 WHO MDS Subtypes

<table>
<thead>
<tr>
<th>Subtype</th>
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<tbody>
<tr>
<td>MDS with single lineage dysplasia</td>
</tr>
<tr>
<td>MDS with multilineage dysplasia</td>
</tr>
<tr>
<td>MDS with Ringed Sideroblasts</td>
</tr>
<tr>
<td>MDS with RS with single lineage dysplasia</td>
</tr>
<tr>
<td>MDS-RS with multilineage dysplasia</td>
</tr>
<tr>
<td>MDS with isolated del(5q)</td>
</tr>
<tr>
<td>MDS with excess blasts</td>
</tr>
<tr>
<td>MDS-EB-1</td>
</tr>
<tr>
<td>MDS-EB-2</td>
</tr>
<tr>
<td>MDS, unclassifiable</td>
</tr>
<tr>
<td>With 1% blood blasts</td>
</tr>
<tr>
<td>With single lineage dysplasia and pancytopenia</td>
</tr>
<tr>
<td>Based on defining cytogenetic abnormality</td>
</tr>
<tr>
<td>Refractory cytopenias of childhood</td>
</tr>
</tbody>
</table>

Chromosomal Abnormalities that diagnose MDS in Absence of definitive morphological criteria

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>Frequency, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 or del(5q)</td>
<td>10-15</td>
</tr>
<tr>
<td>7 or del(7q)</td>
<td>10</td>
</tr>
<tr>
<td>t(17q) or t(17p)</td>
<td>2-3</td>
</tr>
<tr>
<td>del(12p) or t(12p)</td>
<td>1-2</td>
</tr>
<tr>
<td>del(11q)</td>
<td>1-2</td>
</tr>
<tr>
<td>−13 or del(13q)</td>
<td>1-2</td>
</tr>
<tr>
<td>del(19q)</td>
<td>1</td>
</tr>
<tr>
<td>idic(3)(q13)</td>
<td>1</td>
</tr>
<tr>
<td>inv(3)(q21q26.2)</td>
<td>1</td>
</tr>
<tr>
<td>t(8;9)(p23;q24)</td>
<td>1</td>
</tr>
<tr>
<td>t(9;21)(q22.2;q22.1)</td>
<td>&lt;1</td>
</tr>
<tr>
<td>t(11;19)(q23;p13.3)</td>
<td>&lt;1</td>
</tr>
<tr>
<td>t(12;13)(p11;q23)</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

Pathogenesis

- Unclear (?) becoming clearer
  - Involves the stepwise acquisition of oncogenic driver mutations
    - Thought to derive from a single transformed hematopoietic progenitor cell
    - >90% cases are associated with ≥ 1 driver mutation
  - Immune dysregulation
  - Abnormal marrow microenvironment
  - Alterations in DNA methylation/histone function
**Treatment**

Patient diagnosed with lower-risk MDS per IPSS (score < 1.0) or IPSS-R (score < 4.0)
- No transfusion needs, good quality of life
- Observer, follow blood counts every 1-6 months depending on stability
- Anemia (Hgb < 10 g/dl and/or transfusion – dependent, symptomatic)
- Thrombocytopenia (<20k/L or <50k/L with bleeding)
- Start anti-thymocyte globulin or hypomethylating agent or enroll into clinical trial
- Start erythropoiesis stimulating agent or blood transfusions
- Start thrombopoietin agonists or platelet transfusions or enroll into clinical trial
- Start lenalidomide or enroll into clinical trial
- Start hypomethylating agent or enroll into clinical trial

**Anemia and Survival**

- 1000 newly diagnosed patients with low and INT-1 risk MDS enrolled in European LeukemiaNet MDS registry (EUMDS)
  - 14 countries
  - Median age = 74 years
  - Most patients died without disease progression (higher risk/AML)
  - Infectious and cardiovascular
- The mortality rate in transfusion dependent patients was 24% vs 5% in transfusion independent patients
  - Transfusion dependent patients with disease progression had a higher mortality rate than those who were not transfusion dependent at disease progression (66% vs 32%)
  - Transfusion dependent patients without disease progression and a serum ferritin > 1000 μg/L had a higher mortality rate 56% vs 21% (HR 4.79, 95% CI 2.56-8.96) than transfusion independent patients
- The degree of anemia appears to have an impact on OS and leukemia free survival

**Erythropoietin Stimulating Agents**

- Erythropoietin induces globin gene expression and promotes late erythroid differentiation
- Who responds?
  - Patients with lower risk MDS without ring sideroblasts had a higher probability of response
  - Higher response rates in patients without a prior transfusion need
  - Higher response in those with pre-treatment serum epo levels < 150-200

<table>
<thead>
<tr>
<th>Serum Epo Points</th>
<th>PRBCs/month Points</th>
<th>Total Score</th>
<th>Likelihood of response</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 100</td>
<td>+2</td>
<td>-1 to +1</td>
<td>74%</td>
</tr>
<tr>
<td>100-500</td>
<td>+1</td>
<td>-2</td>
<td>23%</td>
</tr>
<tr>
<td>&gt; 500</td>
<td>&gt; 2 Units</td>
<td>-1</td>
<td>7%</td>
</tr>
</tbody>
</table>

Predictive model for response to erythropoietin and GCSF
Based on serum epo level and RBC transfusion requirement

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<table>
<thead>
<tr>
<th><strong>Erythropoietin Stimulating Agents</strong></th>
<th><strong>Iron Overload</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Response can take 8 weeks or more</td>
<td>• Begins prior to patients becoming red cell transfusion dependent</td>
</tr>
<tr>
<td>• Duration of response and time to transfusion dependency is longer in patients treated within 6 months of diagnosis vs after 6 months</td>
<td>• Ineffective erythropoiesis suppresses hepcidin production in the liver → unrestrained intestinal iron uptake due to lack of inhibition of ferroportin (iron channel on basolateral surface of enterocytes)</td>
</tr>
<tr>
<td>• Erythroid response to darbepoietin 56% at 24 weeks in lower risk MDS patients</td>
<td>• Iron toxicity may not only depend on the degree of iron accumulation but also on the extent of exposure to non-transferrin bound iron → increased oxidative stress</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Iron Chelation</strong></th>
<th><strong>Higher Risk Patients</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Above a serum ferritin of 1000 ng/mL there is a dose dependent impact on OS 30% greater risk of death for every 500ng/mL increase in ferritin above 1000 ng/mL</td>
<td>• Early initiation of hypomethylating agent</td>
</tr>
<tr>
<td>• Recommendations for chelation are mostly based on expert opinion</td>
<td>• Azacitidine or decitabine</td>
</tr>
<tr>
<td>• Patients with a transfusion history of at least 20 or 25 units of PRBCs and serum ferritin &gt; 1000</td>
<td>• CR rate of approximately 20%</td>
</tr>
<tr>
<td>• Focus on patients with lower-risk MDS who may have a longer life expectancy and will therefore receive long-term transfusion therapy</td>
<td>• 21 months versus 13 months of AML transformation when compared to Best Supportive Care</td>
</tr>
<tr>
<td>• MRI is able to diagnose iron overload</td>
<td>• Screen for HLA matched donor at diagnosis</td>
</tr>
</tbody>
</table>

Malcovati L et al Haematologica 2006; 91: 1588-90
Role of Allogeneic transplantation

- 3rd most common indication for allogeneic stem cell/bone marrow transplantation

- Cutler et al. developed decision model to understand how treatment decisions affect overall outcome in patients with newly diagnosed MDS
  - Low/Int-1 IPSS patients – delay until progression
  - Int-2/High risk IPSS patients – early transplantation


Special Case

- A 52 year old female was found to have a new diagnosis of Stage III breast cancer and due to history of high risk family cancer, she sought genetic counseling.
  - She underwent testing which included next generation sequencing of the blood.
  - Results showed a \textit{DNMT3A} mutation and her peripheral blood counts were normal at time of testing
  - This result was consistent with Clonal Hematopoiesis of Indeterminate Potential (CHIP)

Clonal Hematopoiesis of Indeterminate Potential

Condition characterized by the presence of a somatic mutation associated with a hematologic malignancy in the absence of definitive diagnostic criteria for neoplasm


Idiopathic cytopenias of undetermined significance (ICUS)

- Describes patients in whom MDS is possible but not proven
  - Must have relevant cytopenia in one or more lineage *hemoglobin <11 g/dL, neutrophil count <1500, platelet count <100,000 that persists for 6 months, cannot be explained by other disease and does not meet diagnostic criteria of MDS
  - Patients should be carefully monitored

Janis - CHIP is more of a condition than a test, so I think this belongs in On Target (do we need to label all slides?)

Harty, Patrick, 5/21/2020
Special case continued

- She underwent treatment for her breast cancer with systemic chemotherapy and surgery.
- Approximately 5 years later, she began developing pancytopenia with WBC of 1.5, Hgb 10.0, and platelet count of 89,000. Her MCV was 105.
- She underwent a bone marrow biopsy for work-up and was consistent with MDS-EB-1 with 9% blasts.
- Cytogenetics were complex with NGS showing a new TP53 mutation along with her known DNMT3A mutation.
- Diagnosis was consistent with therapy-related MDS and patient was initiated on azacitidine

Special case continued

- The patient underwent bone marrow re-assessment after 2 cycles of therapy and was found to have progression to AML with 24% blasts.
- Bone marrow biopsy showed no change in cytogenetics or NGS results from prior testing.
- She is now undergoing treatment with liposomal daunorubicin and cytarabine for AML with MDS-related changes.

Conclusions

- MDS is a heterogeneous disease
  - Mutational analysis will likely improve our ability to risk stratify patients better and potentially give more targeted therapeutics
  - Consideration of ESA therapy in patients with low risk disease with anemia only is reasonable
  - Consider lenalidomide in patients with 5q abnormalities
  - Consider luspatercept in MDS with Ringed Sideroblasts who are transfusion-dependent and not/lost response to ESA therapy
  - 5-azacytidine is the only available hypomethylating agent with a proven survival advantage
  - Consider BMT referral in patients with higher risk disease