Review of Myelodysplastic Syndrome (MDS)

1. Epidemiology
   a. Relatively rare: about 5 new cases per 100,000 annually in U.S.
   b. Steep increase in incidence in advanced age (median age at diagnosis is 70-75)
   c. Risk factors: age, prior cytotoxic therapy (chemo, radiation), smoking?
      i. Association with other hematologic disorders, especially aplastic anemia and paroxysmal nocturnal hemoglobinuria (PNH)
      ii. Some genetic disorders with predisposition for MDS: Fanconi anemia, dyskeratosis congenita

2. Clinical manifestations
   a. Symptoms from cytopenias: fatigue, recurrent/opportunistic infection, bruising, etc.
   b. Autoimmune manifestations (e.g., arthritis, cutaneous vasculitis) seen in a minority of patients--hints toward possible autoimmune pathophysiology of MDS
   c. Clues from CBC:
      i. Anemia is most common: usually macrocytic with inappropriately low retic count
      ii. Leukopenia with immature forms, but occasionally can see leukocytosis
      iii. Thrombocytopenia, but (again) occasionally can see thrombocytosis (particularly with 5q minus syndrome [see below] and ringed sideroblasts)
      iv. Findings on peripheral blood smear other than low (or high) blood counts:
         1. WBC: hypogranular neutrophils, bilobed neutrophils ("pseudo-Pelger-Huet" cells)
         2. RBC: macrocytosis, basophilic stippling
         3. Platedets: large/giant platelets, hypogranular platelets

3. Diagnosis
   a. Rule out alternative causes: vitamin deficiencies (folate, B12), mineral deficiencies (copper), alcohol use, hypothyroidism, other marrow disorders, etc.
   b. Bone marrow examination is mandatory:
      i. Morphology remains most important component
         1. Pathologist looks for "dysplastic" features
         2. Identifies number of cell lines affected (uni- vs multilineage dysplasia)
         3. Subcategory then assigned based on this information (examples below)
            a. Refractory cytopenia with unilineage dysplasia
            b. Refractory cytopenia with multilineage dysplasia
            c. Refractory cytopenia with ringed sideroblasts
            d. Refractory anemia with excess blasts (i.e., 5-19% blasts; ≥20% blasts = AML)
      ii. Cytogenetics and fluorescence in situ hybridization (FISH) can identify clonal karyotypic abnormalities
         1. Most common abnormalities: 5q deletion, monosomy 7, trisomy 8, 20q deletion
iii. Flow cytometry can identify abnormal expression of certain proteins, but not currently used to make formal diagnosis

4. Prognosis
   a. Most widely-used tool is the international prognosis scoring system (IPSS)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Score</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Bone Marrow Blasts (%)</td>
<td>&lt;5</td>
</tr>
<tr>
<td>Karyotype*</td>
<td>Good</td>
</tr>
<tr>
<td>Cytopenias^</td>
<td>0 or 1</td>
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</tbody>
</table>

   * = Good karyotypes are normal, del 5q, del 20q, loss of Y; poor karyotypes are abnormal 7 or complex (>3 abnormalities); intermediate are all others

   ^ = Cytopenias are defined as neutrophils < 1800/µL, Hgb < 10 g/dL, platelets < 100,000/µl

   i. Points are added up for each variable, giving a composite risk score
      1. Low = 0 points \(\rightarrow\) median survival of about 6 years
      2. Intermediate-1 = 0.5-1 point \(\rightarrow\) median survival of about 3.5 years
      3. Intermediate-2 = 1.5-2 points \(\rightarrow\) median survival of about 1 year
      4. High = 2.5-3.5 points \(\rightarrow\) median survival of about 5 months

      (Note: survival statistics are with supportive care only [see below])

   b. Cause of death: bone marrow failure (about 2/3) vs. acute myeloid leukemia (about 1/3)

5. Treatment
   a. Supportive care: transfusion support, hematopoietic cytokines (G-CSF, EPO)
   b. Goals of systemic therapy: reduce transfusion dependence, prevent evolution to acute myeloid leukemia, prolong survival
      i. Lenalidomide particularly useful in those with deletion 5q ("5q minus syndrome")
      ii. Immunosuppression with anti-thymocyte globulin (ATG) +/- cyclosporine for those with certain characteristics (e.g., low IPSS, hypocellular marrow, young age, short duration of red cell transfusion dependence)
      iii. DNA hypo-methylating agents (azacitidine and decitabine) for all risk groups by IPSS
         1. Azacitidine is the only agent ever shown to improve survival in MDS
   c. Allogeneic hematopoietic cell transplantation remains the only curative option

6. Special case: myelodysplastic/myeloproliferative neoplasms (MDS/MPN)
   a. These have clinical and pathologic features of both MDS and MPN
   b. Treatment and prognosis differ based on subtypes
   c. Examples: chronic myelomonocytic leukemia (CMML), atypical chronic myeloid leukemia (aCML), refractory anemia with ringed siderblasts and thrombocytosis (RARST)

Suggested Additional Reading: