Myelodysplastic Syndrome

• Stem cell clonal disorders characterized by ineffective hematopoiesis and various peripheral cytopenias.
• "Sick Marrow Syndrome"
• Risk of transformation to AML

Pathophysiology:
- Reduced mature cells in periphery due to:
  - 1. Disordered maturation - ineffective hematopoiesis despite adequate numbers of progenitors in BM. (but usually hypercellular).
  - 2. Apoptosis in BM
- 30-40% develop AML

Risk Factors:
- Post-chemo (esp. topoisomerase inhibitors and alkylating agents, mycophenolate - DNA damage)
- Radiation exposure
- Elderly
- DNA Repair Defects (Down’s Syndrome, Fanconi Anemia)
- Incidence: 60/100,000 in >60yrs old.

Clinical Features:
- Insidious onset - usually see pancytopenia.
- Any aplastic anemia symptoms (anemia, thrombocytopenia, neutropenia)
- Classically: Megaloblastic anemia (can be normocytic)
- Infections and bleeding not consistent with peripheral blood counts?
- On Exam:
  - NO Lymphadenopathy
  - NO splenomegaly

Classification: (WHO classification)
- Many categories
  - Variable survival.
  - Many sideroblasts (long survival 69mo)
  - 5q deletion (median survival 160mo - longest)
- Refractory Anemia With Multilineage Dysplasia (survival down to 33mo)
- Blast Numbers:
  - 5-9% Blasts: "Refractory Anemia With Excess Blasts 1" (median survival 18mo)
  - 10-19% Blasts: "Refractory Anemia With Excess Blasts 2" (median survival 10mo)
  - 20% Blasts: AML (in past is "Refractory Anemia with Transformation")
- MDS Unclassified (survival unknown)

Investigations:
- Exclude B12, Folate, Medication effects (i.e. mycophenolate), HIV
- CBC (Anemia + thrombocytopenia + neutropenia.)
- Peripheral Blood film: Shows Dysplastic Features!
  - RBC - macrocytic nucleated with oval shaped RBC (macro-ovalocytes).
  - "Pelger Huetoid Cells" - dumb-bell shaped neutrophils or "glasses" look.
    - "Prince Nez Glasses" Cells - type of eye glasses.
    - Aka hypolobulated neutrophils
- Dysplasia in any cell line.

Bone Marrow:
- Dysplastic, bone marrow can be normo/hypercellular. (depends on cytogenetics).
- Cytogenetics (REQUIRED FOR DX)
  - Many chromosomal abnormalities:
    - i.e. partial or total loss of chromosomes 5,7,Y, or trisomy 8.
• **Prognosis:**
  - **MDS International Prognostic Scoring System (IPSS),** uses 4 factors.
    1. % of bone marrow blasts.
    2. Karyotype (good, intermediate, poor)
    3. Number of cytopenias
    4. Age (<60 or >60)
  - Predicts outcome
  - Calculate IPSS score:
    - 1 - "low" (mean survival 5.7yrs)
    - 2 - "interm. 1" - 1.2 yrs.
    - 3 - "interm. 2" - 3.5 yrs.
    - 4 - "high" - 0.4yrs.

• **Treatment:**
  - Based on risk of transformation to AML
  - **LOW RISK**
    - Supportive (RBC/platelet transfusions)
    - EPO SC weekly
  - **HIGH RISK**
    - Supportive (as above)
    - Stem cell transplant if <65yrs.
    - Epigenetic therapy (DNA methyltransferase inhibitors and histone deacetylase inhibitors).
  - **NOTES:**
    - Transfusions
      - Be careful, at risk of iron overload.
      - Iron chelators (only benefit in primary hemochromatosis), unclear in MDS.
      - Consider if ferritin > 1000 if expected to have long survival.
  - Erythropoiesis Stimulating Agents (ESA)
    - May be beneficial in pts with symptomatic anemia.
    - Useful if EPO count not high.
    - GCSF: may increase erythroid response (in addition to WBC)
    - DO NOT increase risk of progression to AML
  - **Drugs:**
    - Azacitidine & another. - Pyrimidine analogue when compared to standard of care:
      - Better response rate
      - Decrease risk of transformation to AML
      - Improves median overall survival in high risk MDS.
      - Hypomethylating agents (when demethylate, improve differention to myeloid cells).
    - Lenolidomide
      - Effective in making transfusion (70% of pts) independence in 5q- deletion pts.

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**Sideroblastic Anemia**

• **Type of MDS**
  - Stain marrow with iron and counterstain with sapharin.
    - See iron in siderosomes (don't get into nucleus)
    - Called "sideroblasts"
• **Causes:**
  - Can be associated with MDS
  - Congenital
  - Drugs: Chloramphenicol, Isoniazid, Alcoholism
  - Metabolic: Copper Deficiency, Zinc Excess
    - (Both characterized by iron deficiency)

**Chronic Myelomonocytic Leukemia**

• Features of myelodysplastic and myeloproliferative disorder.
  - (CML is a myeloproliferative disorder)

• **Symptoms**
  - Constitutional (Wt loss, nt sweats)
  - Hepatosplenomegaly

• **Dx:**
  - Peripheral Smear (mature monocytes, leukocytosis is common)
  - Monocytes > 1000 (normal 850)

• **Treatment:**
  - Supportive.
  - If WBC too high > 100,000 --> Hydroxyurea, helps constitutional sx and HSM.
  - Hypomethylating agents azacitidine, (limited experience).
  - Young patients (like almost all myelodysplastic syndromes) --> consider for allogeneic stem cell transplant.