Myeloproliferative Disorders (MPDs)

Myelodysplastic Syndrome (MDS)

- **Definition**
  - "age related damage" to BM resulting in a clonal dysplastic disorder of hematopoietic stem cells

- **Epidemiology**
  - 12k/yr therefore more common than AML, >60yo, M>F
  - RFs: 70% idiopathic (increasing age) vs 30% secondary (alkylating/topoisomerase chemo, radiation, organic solvents, congenital syndromes)
  - Only 50% of AML likely had prior MDS vs ~100% of MDS eventually transform into AML if pts do not die from effects of cytopenia
    - NB 25% r/o AML (occurs when MDS cells escape apoptosis and turn AML)

- **S/S**
  - usually asymptomatic and thus diagnosed on routine CBC w/ pancytopenia

- **Dx**
  - PBS (macrocytic anemia, thrombocytopenia but those present are large, hypogranular/dysplastic/hyposegmented neutrophils)
  - BM (certain cytogenetic abnormalities, dysplastic hypo/eu/hypercellular cells w/ increased blasts, ringed sideroblasts, ineffective hematopoiesis)
    - NB nl BM has <5% blasts, MDS has 5-20% blasts, leukemia >20% blasts
  - Very important to rule out folate/VitB12 deficiency

- **Prognostic Classifications**
  - FAB
  - WHO
  - IPSS (most important b/c tells you survival and progression to AML) 4 defined risk groups at diagnosis based on (1) % blasts on BM, (2) type of cytogenetics aka karyotype, (3) # of peripheral cytopenia
    - **Good Karyotypes**
      - Normal (most common 35% of pts)
      - Del(5q) (seen in old females, megakaryocyte w/ one nucleus w/ thrombocytosis, Revlimid is very effective)
      - Del(20q)
      - Del(Y)
    - **Intermediate Karyotypes**
      - +8
      - Del(17p)
    - **Bad Karyotypes**
      - ?

<table>
<thead>
<tr>
<th>Score</th>
<th>Group</th>
<th>Years to Transformation to AML</th>
<th>Median Survival</th>
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</thead>
<tbody>
<tr>
<td>&lt;0.5</td>
<td>Low</td>
<td>3.4yrs</td>
<td>5.7yrs</td>
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<tr>
<td>0.5-1</td>
<td>Intermediate-1</td>
<td>3.3yrs</td>
<td>3.5yrs</td>
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<tr>
<td>1-2</td>
<td>Intermediate-2</td>
<td>1.1yrs</td>
<td>1.2yrs</td>
</tr>
<tr>
<td>&gt;2</td>
<td>High</td>
<td>0.2yrs</td>
<td>0.4yrs</td>
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- **Tx**
  - Supportive Care (transfusions, prophylactic abx, iron chelation etc) but does not alter the underlying disease process
  - Growth Factor (G/M-CSFs are controversial b/c they might increase progression to AML thus rarely used, Epo is generally used only for palliative purposes b/c of expense)
  - Immunomodulators (better quality of life and decreased leukemic transformation compared to supportive care)
    - Proteasome Inhibitors: lenalidomide (Revlimid) = good for Low/Int-1 IPSS MDS
    - Hypomethylating Agents: 5-azacitidine (Vidaza) and decitabine (Dacogen) = good for Int-2/High IPSS MDS
  - Incurable except HSCT = when to use this is unclear?

Acute Myelogenous Leukemia (AML)

- **Stain:** Sudan Black & Myeloperoxidase & Esterase
- **RFs**
  - Idiopathic (most common)
  - antecedent hematologic disorder (esp MDS, MPD, aplastic anemia, PNH) more aggressive and less responsive
  - pts who survive a prior cancer often develop AML b/c of the chemotherapy used: 4yrs if alkylation agent vs 10mo if topoisomerase-II inhibitors, more aggressive and less responsive
  - ionizing radiation (atomic bomb in Japan)
  - organic solvents (benzene, smoke)
  - genetic (trisomy 21, monosomy 7, Klinefelters, Fanconi, Patau, Bloom, NF, various polymorphisms of enzymes that metabolize carcinogens, AML1 gene mutation, CEBPA gene mutation)
- **Epidemiology**
  - 1st Adult ~65yo (less acute Sx over wks-mos)
  - 2nd Child <1y (more acute Sx over days-wks)
- 12k cases/yr, 90% of adults leukemias

- **Unique Symptoms**
  - Extra-Medullary Leukemia (EML) esp M5
    - CNS = “CNS Leukemic Infiltration”
    - Mass anywhere in body = "Granulocytic Sarcomas" aka “Chloroma”
    - Gingiva = “Gingival Leukemic Hypertrophy”
    - Skin = “Leukemia Cutis”
    - NB sometimes pts present w/ only EML w/ no peripheral or BM involvement, others present concurrently, while others present after a diagnosis of AML has been made and if so it almost always heralds a relapse
    - NB can progress to AML if not treated with chemo (same chemo used to treat AML), primarily seen in children, more common in monocytic forms of AML
  - DIC esp APML
  - Production of lysozyme which damages renal tubules

- **Classification**
  - PBS: Auer Rods (eosinophilic cytoplasmic needles in neutrophils)

| FAB Classification (NB no longer used except for M3) |
|----------------|------------------|
| **Type** | **Frequency** |
| M0     | <5%             | No Differentiation |
| M1     | 20%             | Minimal Differentiation |
| M2     | 25%             | Full Differentiation |
| M3     | 10%             | Acute ProMyelocytic Leukemia (APML) |
|        |                  | - poor response to conventional AML Tx but dramatic response to retinoids/arsenics hence most favorable subtype of AML |
|        |                  | - 90%: (15;17) joins PML (ProMyelocytic Leukemia) gene (causes cancer) and RAR-alfa (Retinoic Acid Receptor) gene (enzyme that when active causes NO maturation) vs 10%: (15;17) joins RAR-alfa gene w/ PLZF, NUMA, STATS or NPM genes which is important b/c retinoid resistant |
|        |                  | - Auer Rods are classically seen in M3 but can be seen in M1 and M2 |
|        |                  | - High r/o DIC but then it was found that low dose heparin prevented DIC (very complicated mechanism) |
|        |                  | - Tx: All Trans Retinoic Acid (ATRA): causes cellular differentiation and maturation of promyelocytes which subsequently undergo apoptosis, SEs: Retinoic Acid Syndrome (as cells mature they become sticky and clog vessels in (1) lungs looking like a PNA w/ pleural effusions, (2) kidneys looking like AKI, etc, Tx: steroids) NB there is some evidence that ATRA is effective against SCC, Kaposi, Metastatic RCC vs Arsenics: similar to ATRA, toxicity (prolonged QT, peripheral neuropathy, similar to RAS) |
| M4     | 20%             | Primarily Granulocytic Differentiation |
| M5     | 20%             | Primarily Monocytic Differentiation |
| M6     | 5%              | Primarily Erythrocytic Differentiation |
| M7     | <5%             | Primarily Megakaryocytic Differentiation |

- **WHO Classification**
  - AML w/ Recurrent Genetic Abnormalities (90%)
  - MDS Related AML
  - Chemo Related AML
  - AML not otherwise categorized

- **Treatment**
  - Induction Chemo
    - Non-M3 AML: anthracyclines (-rubcin) x3d + cytarabine (AraC) x7d = "3 + 7" vs. M3 AML: similar to Non-M3 just add All-Trans-Retinoic Acid (ATRA) and Arsenic
at about 7d after chemo check for complete remission (CR) = <5% blasts in BM and 0% blasts and normal peripheral counts in peripheral smear

- if +CR (50%) then proceed w/ consolidation therapy
- if -CR (50%) then proceed w/ re-induction if still no CR then consider HSCT

- Consolidation b/c occult dz exists even if “CR” - Chemotherapy (Ara-C x12d Q6wks x8) and then pts undergo eval for HSCT
- Maintenance
- No maintenance therapy unless APML
- Other
- Clinical Trials: gemtuzumab (Mylotarg) antibody against CD33, SEs: hepatic VOD

Prognosis
- CR achieved in 75% of pts <60yo and 45% of pts >60yo w/ overall survival of 50% in pts <60yo w/ good prognostic factors to 10% in pts >60yo w/ poor prognostic factors
- Poor Prognostic Factors
  - >60yo, poor performance score, +CD34, +MDR-1 (Multidrug Resistant Protein), WBC>30k, unfavorable cytogenetics (any abnormal karyotype esp -5 and -7, certain translocations like t(6;9)) t(9;22) = Philadelphia Chromosome (unlike in CML this translocation portends a WORSE prognosis even though you have another therapeutic modality), antecedent hematologic problems (MDS, MPD, etc), mutations (FLT3, MLL, BAALC), absence of Auer Rods, LDH>2.9ULN, AA, extramedullary dz, CD34 negative

- Good Prognostic Factors (opposite in addition to below)
  - APML b/c responds very well to ATRA, favorable cytogenetics (translocations like t(8;21), inv(16)/t(16;16), t(15;17)), mutations (NPM1, CEBP)
  - Check these mutations with PCR
    - NPM1 Mutation: Nucleophosmin-1 gene ???
    - FLT3 Mutation: FMS-like tyrosine kinase 3 gene producing internal transmembrane duplications and constitutive activation of receptor tyrosine kinase are associated with poorer survival; however, the identification of such specific molecular abnormalities may eventually permit development of compounds targeted at these changes, similar to the use of the tyrosine kinase inhibitor, Imatinib, in patients with CML

Relapse
- Chemotherapy followed by HSCT (for all AML urgently send pt to tertiary referral center for HSCT, there are three types of AML where HSCT is not always necessary: (1) APML, (2) inv(16), (3) t(8;21))

Myeloproliferative Disorders (MPDs)
- Clonal expansion of myeloid lineage cells (WBCs, Plts, RBCs) and stromal cells (fibroblasts) BUT unlike MDS/AML there is (1) ongoing differentiation into mature blood elements, (2) NO peripheral blood cytopenias, (3) NO cellular dysplasia, (4) occurs in slightly younger pts (50-65yo) not >65yo, (5) different genetic mutations (refer below), (6) low risk (except for CML) of AML transformation (~10% over several decades)
- Common genetic activating mutation in almost all of the MPDs is of the gene that codes for JAnus Kinase-2 (JAK-2)
  - CML 0% sensitivity
  - PV 95% sensitivity
  - ET 40% sensitivity
  - AMM w/ MF 50% sensitivity
  - NB seen in some non-MPD problems like AML
- Common PBS Findings: Basophilia, Eosinophilic Myelocytes, Mixed Baso-Eos Granules, Giant Platelets
  - S/S: splenomegaly
  - Other rare MPDs: CEL, Systemic Mastocytosis, etc

Chronic Myeloid Leukemia (CML)
- Mechanism
  - t(9;22) = Philadelphia Chromosome = two protooncogenes joined together (abl on 9 to bcr on 22) resulting in one gene that is now an oncogene forming a constitutive fusion tyrosine kinase
- Two Phases
  - Chronic Phase: asymptomatic, lasts 2yrs if unTx or 4yrs if on Hydroxyurea or Syrs if on IFN or ?yrs if on Imatinib, <10% blasts in BM, pts typically presents in this stage with a leukocytosis anywhere b/t 20k-100k with no blasts but just slight immaturity aka left shift, How do you differentiate CML and just a normal leukemoid reaction? (refer to general heme notes)
  - Accelerated Phase: in b/t, characterized by worsening eosinophilia/basophilia, additional cytogenic abnormalities, more difficult to Tx, etc
  - Blast Crisis: death in weeks if not Tx, >20% blasts in BM, conversion into AML (2/3) or ALL (1/3)!!!, increasing anemia and thrombocytopenia and additional cytogenic abnormalities, bone pain, F, night sweats, weight loss, worsening leukocytosis w/ less mature cells despite Tx, worsening splenomegaly, increased BM fibrosis, this type of secondary AML is much worse than primary
- Treatment
  - Historical: bulsulfan (Myleran) then hydroxyurea (Hydra) then alpha-iFN (?)
although chronic leukemias are typically incurable, CML is actually curable with tyrosine kinase inhibitors like imatinib (Gleevec) and if pts are intolerant or become resistant then use dasatinib (Sprycel). Currently many pts are still living after the initial trials with TKI. SEs: muscle cramps, mild N, transient leukopenia, rash, hepatotoxicity, fluid retention.

HSCT only definitive cure, better if done early on.

Follow marrow cytogenetics, peripheral number of bcr/abl transcripts, and PBS WBC to assess response.

Prognosis

Good Factors: smaller spleen, fewer blasts, <45yo, plt >70k

Polycythemia Vera (PV)

Mech

Clonal hematopoietic progenitor cell resulting in overproduction of phenotypically normal RBC/platelets in the absence of a recognizable stimulus.

Unique S/S

Hyperviscosity Phenomenon = erythromelalgia, headache, dizzy, weak,aquagenic pruritis, vision problems, dyspnea, facial plethora, HSM

Thrombotic Phenomenon = DVT, CVA, MI, portal vein thrombosis

Bleeding Phenomenon = GI or GU bleeding, ecchymoses, epistaxis

NB eventually a paradoxical anemia occurs because of damaged RBC.

Dx

Increased RBC Mass (Hgb and Hct will be elevated but you should never make a dx based on these values rather order an actual "red blood cell mass")

No Cause of Secondary Erythrocytosis with Low Epo (refer to general heme notes)

Other: Splenomegaly, thrombocytosis >400k/L, BM showing panmyelosis w/ pre-eminent erythroid/megakaryocytic proliferation, Leukocytosis >12k/L

Tx

Phlebotomy Q2-4months w/ goal Hct <42/45 essentially causing IDA

Add Hydrea/Anagrelide if symptomatic.

Prognosis

Incurable but 65% are alive after 15 years, usually slow/indolent over many years, death from leukemic transformation, CV dz, or AMM w/ MF transformation.

Essential Thrombocytosis (ET) (most common MPD, least aggressive)

Symptoms (these are seen in clonal thrombocytopenia not in reactive, pts usually either bleed or clot not both)

Arterial/Venous Thrombosis in 30% of pts

Erythromelalgia (burning sensation, warmth, redness, etc of the distal extremities esp fingers/toes that is relieved w/ cold exposure 2/2 microvascular occlusion)

Acral Dysesthesia (aka of the extremities)

Bleeding (b/c even though there are many of them often they don't function as well and also they bind vWF therefore also check Ristocetin Cofactor A)

Splenomegaly in 50% of pts

Pruritus (for some unknown reason)

Livedo Reticularis

Headache

Vision Symptoms

4% conversion to AML

Differential

Primary/Clonal

Smear: giant hypogranular plts w/ abnl fxn

BM Bx: giant dysplastic megakaryocytic hyperplasia, fibrosis

Sx: above

Labs: JAK2 mutation

Secondary/Reactive

Dx: >600k plts on PBS + megakaryocytic hyperplasia on BM + no conditions associated w/ reactive process + normal RBC mass + NO Philadelphia chromosome + Ni iron staining on BM

Primary/Clonal (>1,000,000/microliter)

Smear: giant hypogranular plts w/ abnl fxn

BM Bx: giant dysplastic megakaryocytic hyperplasia, fibrosis

Sx: above

Secondary/Reactive (<1,000,000/microliter)

Smear: nl plts

BM Bx: normal megakaryocytes

Sx: usually none aside from 5x associated w/ underlying systemic disease.
- Labs: elevated APRs

- Treatment
  - Asymptomatic
    - Low Thrombotic Risk: <60yo and plt <1,500k and NO h/o thrombosis and NO CV RFs and no Sx = nothing
    - Int Thrombotic Risk: in b/t = consider Tx below
    - High Thrombotic Risk: >60yo or plt >1,500k or h/o thrombosis or CV RFs or Sx
      - Start aspirin 81mg
      - Start cytoreduction w/ goal plt of<400k
        - 1° hydroxyurea (Hydrea)
          - Mechanism: unknown
          - Problem: ~3% r/o acute leukemia with long term use aka leukemogenic
        - 2° anagrelide (Agrylin)
          - Mechanism: unknown
          - Problem: HA, vasodilatory, positive inotropic, fluid retention, palpitations, Afib, HF effects
          - NB in comparison to Hydrea, Agrylin has equivalent platelet reduction but more thrombotic and hemorrhagic complications and myelofibrotic BM transformation therefore used as a 2nd line
        - 3° alpha-interferon (IFN)
  - Symptomatic
    - Immediate aspirin
    - Immediate cytoreduction
    - Immediate platelethpheresis

- Agnogenic (aka Idiopathic) Myeloid Metaplasia w/ Myelofibrosis (AMM w/ MF)
  - Mech
    - Neoplastic atypical megakaryocytes release PDGF and TGF-B which stimulate fibroblasts to secrete collagen resulting in fibrotic obliteration of BM (“dry tap”) and extramedullary hematopoiesis in liver and spleen (thus massive hepatosplenomegaly) but still there is pancytopenia
  - Dx
    - PEx: HSM
    - BM: aspirate (dry tap), Bx (fibrosis)
    - PBS: “Leuko-erythro-blastic smear” = nucleated RBCs w/ tear drops RBCs and large abnl platelets and immature myeloid cells
  - Tx
    - Supportive but there is some evidence that thalidomide/androgens and HSCT is helpful but overall median survival is 4yrs and death from leukemic transformation, BM failure, and portal HTN