Acute Myeloid Leukemia (AML)

**Introduction:**
- 80% of all acute leukemia in adult,
- ↑ incidence in older population (median age = 67 yrs)
- 5-yr survival <50% in adults age <45yrs; <5% in patients age >65 yrs.

**Risk Factors:**
1. Genetics & Congenital Factors:
   - AR: MDS with monosomy 7.
   - Familial syndrome of erythroleukemia
   - AD: Aspirin-like platelet disorder (germline mutation in AML-1 gene)
   - Down syndrome (trisomy 21):
     - → ↑ risk (10-18 fold) for AML
     - → ↑ incidence of a transient myeloproliferative disease (TMPD), a/w trisomy 8.
     - → ↑ M7, a/w GATA-1 gene mutation (TF involved in megakaryocyte development).
     - → ↑ response to to cytarabine (↑ intracellular metabolism of cytarabine to cytarabine triphosphate in Down syndrome)
   - Kostman's syndrome (infantile agranulocytosis): Mutation in the G-CSF receptor on chromosome 1p35-p34.3.
   - Diamond-Blackfan anemia: congenital hypoplastic anemia & growth retardation.
   - Bloom syndrome:
   - Fanconi anemia
   - Wiskott-Aldrich syndrome (ataxia telangiectasia)
   - Klinefelter (XXY and variants)
   - Patau (trisomy 13)

2. Therapy-related AML (t-AML): 10-20%.
   - Topoisomerase II Inhibitors:
     - * No MDS phase; latency → 1-3 yrs
     - * Monocytic morphology
     - * a/w translocation between 11q23 (MLL gene) and a varying partner: → t(6:11), t(9:11), t(11:19), or 21q22/RUNX1

   - Alkylating Agents:
     - * Melphalan & nitrosoureas (prolonged exposure & high dose)
     - * Prior MDS phase; latency → 5-10 yrs after exposure
     - * a/w monosomy 5, 7, or 8.

**UpToDate:**
1. FDA approves Enasidenib (idhifa) in relapsed or refractory acute myeloid leukemia with specific mutations in IDH2 gene (8/1/2017).

2. FDA approves liposome-encapsulated combination of daunorubicin and cytarabine (Vyxeos) for the treatment of adults with newly diagnosed therapy-related acute myeloid leukemia (AML) or AML with myelodysplasia-related changes (AML-MRC), two types of AML having a poor prognosis (8/3/2017).
3) Radiation: ionizing radiation
   - 5-10 yrs latency
   - Younger = more susceptible

4) Prior hematological disorders:
   - MDS
   - P. vera
   - CML
   - Primary thrombocytosis
   - Paroxysmal nocturnal hemoglobinuria (PNH)

**Biology:**

A. Cytogenetics Syndrome and Association
   - inv(16) (p23;q22) and t(16;16) (p13; q22) in M4 with eosinophilia
   - t(6:9) (p23;q34) with basophilia
   - 11q23 with MLL rearrangement (infant ALL & therapy-related leukemia)
   - t(1:22) (p13;q13) or 3(q21; q26) in (M7)
   - inv (3) (q21;q26) or t(3;3) (q21;q26) and thrombocytosis
   - t(8;21) (q22;q22) and chloroma
   - monosomy 7 and diabetes insipidus

B. Cytogenetics and Drug Sensitivity:
   - t(8:21), inv (16), core binding factor leukemia: sensitive to cytarabine
   - APL: sensitive to anthracycline
   - chrom 7 abn: sensitive to hypomethylating agent

**Symptoms:**

1). Hyperleukocytosis
   - In microgranular APL & AML with monocytic differentiation
   - inv(16) and inv (16) (p13;q22)
   - WBC >100,000 myeloblasts/mcl at increased risk of leukostasis.

2) Coagulation abnormalities:
   - Abnormal platelet function
   - Consumptive coagulopathy (APL>M5, M4)

3) Metabolic abnormalities

4) Hepatomegaly/Splenomegaly (30%)

5) FAB (M5):
   - Increased incidence of soft tissue involvement, e.g. skin rash (leukemia cutis), CNS involvement (2-3%).
   - Typhlitis (mimics appendicitis)
   - Extramedullary presentation/Myloid sarcoma/chloroma:
      * rare, can occur before leukemia phase
      * FAB M5, t(8:21), CD56+ (neural crest adhesion molecule)
      * high peripheral blast count

6) FAB (M7):
   - Increased marrow fibrosis is common
   - Mediastinal germ cell tumors
- Tumor lysis syndrome
- Renal tubular dysfunction

**Diagnosis:**

**A). Diagnostic evaluation**
- Bone marrow biopsy: flow cytometry, pathology
- Assess prognostic factors (cytogenetics and molecular mutations)
- Special note:
  * M5 with t(9:11) - hyperleukocytosis and tissue infiltration
  * M7 - dry tap, positive CD41, CD61, t(1:22) in children, abnl chr 3,5,7 in adult
  * Auer rods in myeloblasts in 30-45% of patients (elliptical cytoplasmic inclusions)

**B). FAB Classification:** Based on morphology and IHC staining; blast>30%
- M0: Acute myeloblastic leukemia, undifferentiated, 5-10%, MPO<3%
- M1: Acute myeloblastic leukemia, without maturation, 15-20%, MPO>3%, <10% maturation beyond blast stage
- M2: Acute myeloblastic leukemia, with maturation, 25-30%
- M3: Acute promyelocytic leukemia (APL), 10-15%, MPO >3%, >10% maturation beyond blast stage
- M4: Acute myelomonocytic leukemia, 10-20%
- M4 eos: Acute myelomonocytic leukemia with eosinophilia, 5%
- M5: Acute monocytic leukemia, 10-20%
- M6: Acute erythroid leukemia (erthroleukemia), 5%
- M7: Acute megakaryoblastic leukemia, 5%

**C). WHO:** incorporated cytogenetics information; Blast >20%
- AML with recurrent genetic abnormalities
- AML with myelodysplasia-related changes
- Therapy-related myeloid neoplasms
- AML, not otherwise specified.
- Myeloid sarcoma
- Myeloid proliferations related to down syndrome
- Blastic plasmacytoid dendritic cell neoplasm

**Pathology:**

**A) Immunophenotype:**
- Common: CD13+, CD33+, CD117+ (c-kit); often CD11+
- M0: Co-expression of myeloid, nonlineage-restricted lymphoid markers (CD2, CD7, CD4, CD19) & Tdt
- M4 & M5: CD64(+) & CD14(+)
- M6: Glycophorin A (+)
- M7: CD41(+) & CD61(+)
- Note:
  * CD34(+): unfavorable
  * B (CD19) or T (CD7) lymphoid markers are occasionally expressed; may be associated with 11q23, IgH rearrangement or T-cell receptor gene rearrangement

**B) Risk Groups:**

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<tr>
<th>Risk Profile</th>
<th>Cytogenetics</th>
<th>Molecular Genetics</th>
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<table>
<thead>
<tr>
<th>Class</th>
<th>Karyotype/Prognosis</th>
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<tbody>
<tr>
<td>Favorable</td>
<td>t(15:17) PML-RARA, t(8:21) RUNX1-RUNX1T1, inv 16, t(16:16) CBFB-MYH11, Normal karyotype Mutated NPM1 w/o FLT3-ITD, Normal karyotype Mutated CEBPA w/o FLT3-ITD</td>
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<td>Intermediate</td>
<td>Other normal karyotype t(9:11) MLLT3-MLL, Trisomy 8</td>
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<tr>
<td>Poor</td>
<td>t(6:9) DEK-NUP214, inv(3) or t(3:3) RPN1-EVI1, t(v;11q23) MLL rearranged, del 5 or 7; or any monosomy complex karyotype</td>
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<td>Very Poor</td>
<td>&gt; two monosomies one monosomy + another structural change</td>
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Note:

** Gene mutations:
- Good: NPM1 (20-30%), CEBPA (4-15%)
- Poor: FLT3 (15-30% ITD mutation or 5-10% point mutation); c-kit mutation; MLL gene mutation (7%)

** Core binding factor leukemia (CBF)
- t(8:21), inv (16), t(16:16)

C) Subclass of AML:
1. AML t(8:21):
   - Most common in children; 18% of all acute leukemia, and in 40% of M2 with abnormal karyotype
   - In adult, median age=25-30 yrs
   - Favorable prognosis in adult, poor prognosis in children
   - Gene fusion between AML1 gene (chrom 21) and ETO gene (chrom 8).
   - Most common a/w extramedullary disease (EMD), which is also a/w CD56 expression.
   - EMD and loss of sex chromosome have poor prognosis.

2. Inv (16) & t(16:16)
   - Common in M4 (23%)
   - Excessive or morphologically abnormal bone marrow eosinophils
   - CBFB/MYH11 fusion protein
   - Favorable prognosis
Prognosis:

- Poor Prognosis Factors:
  - Age >60
  - WBC >100,000/ul at presentation
  - FAB M6, M7
  - Risk group as determined by cytogenetics and molecular mutations.

3. AML Rearrangements of 11q
   - 11q23 in 35% of pts with M5 and in 50% of those with poorly differentiated monoblastic type (M5a), mainly in children
   - Translocation of 11q23 involve the MLL gene (also called ALL1 or HRX).

4. AML t(3:3) & inv (3):
   - 3-4% of all AML cases
   - a/w thrombocytosis
   - Increased megakaryocytes & micromegakaryocytes in the bone marrow
   - Abnormal EVI1 gene located at 3q26

Tx Principle:

A. Induction therapy for pts <60yrs

1). Tx: "7+3": → Intensive Anthracycline (daunorubicin or Idarubicin) x 3 days, plus standard dose cytarabine (100mg/m2) x 7 days.
   - High dose daunorubicin (90 mg/m2): → ↑ CR and OD in pts < 60yrs with good and intermediate risk group as compared to 45mg/m2 dosing. But for pt positive for FLT3-ITD, → high dose daunorubicine will cause a worse survival.
   - Idarubicin or mitoxantrone can substitute for daunorubicin, → ↑ remission rate but OS benefit.
   - Cytarabine: use standard doseing (100mg/m2) for induction.

2) Post-induction monitoring: √ BM biopsy 7-10 days after completion of induction therapy.

B. Post-induction therapy: Consolidation

1) Good-Risk AML: → HiDAC (3gm/m2) x 3-4 cycles, rather than standard dose cytarabine or SCT.
   * Core-binding factor (CBF) leukemia: → particularly sensitive to HiDAC, with 44% DFS at 4yrs in pts <60yrs.
   * Auto-SCT: → ↑ DFS compared to HiDAC, but no OS benefit.

2) Intermediate-Risk AML: → HiDAC or SCT (allo)

3) Poor-Risk AML: → Allo-SCT.
   - No advantage to giving one or more cycles of consolidation therapy prior to allo-SCT as long as the transplant is not delayed more than several weeks after remission induction.
   - HiDAC = standard dose AraC in transplantation setting.

C. Therapy for AML in Older Adults (>60yrs):
1) Reason for resistant in elderly:
   - 50% have monosomy 5 or 7
   - Complex karyotypes
   - MDR1 at presentation (70% vs 30%)
   - Trilineage dysplasia

2) Induction for elderly (>60yrs):
2.1 Good or Intermediate-Risk AML, ECOG<2: → "7+3" induction w/o dose reduction

2.2 Indolent AML, Severe Comorbidities, High-Risk AML: → supportive care, rather than induction chemo. Or Rx low dose cytarabine or hydroxyurea if needed.

3) Consolidation for Pt (>60yrs)
3.1 "5+2" Standard: Low-dose Daunorubicin (30 to 45 mg/m2) x 2 days & low-dose Cytarabine (100mg/m2) x 5 days
   * HiDAC is not effective
   * ? nonmyeloablative allo-SCT

3.2 Other Options:
   - Clofarabine (intermediate intensity), Hypomethylating agents, Clinical trial.

D. Therapy for Relapsed or Refractory AML (<60yrs):
1) If CR1>1yr: → re-induction with "7+3"
2) If CR1<1yr: → allo-SCT (prefer myeloablative over nonmyeloablative SCT, prefer HLA-matched sibling. If no donor available, consider auto-SCT.
   * Auto-SCT rarely used in 1st relapse, but useful for consolidating second remission
   * Salvage chemo:
     High dose AraC=Mitoxantrone + Etoposide= Etoposide + Cyclophosphamide= FLAG/Ida

3) Relapse after allo-SCT: mOS=3-4 months
   - Second SCT
   - DLI NOT effective in relapse AML.
   - Clinical trial

E. Mgt for Hyperleukocytosis and Leukostasis:
   - Prefer induction chemo with TLS prophylaxis of TLS (allopurinol and IVF), rather then leukopheresis
   - If unable to give chemo immediately, do the following:
     * If pt asymptomatic, → Rx hydroxyurea 2-4gm PO Bid, until WBC <50,000
     * If symptomatic, → start leukopheresis in combination with hydroxyurea

Follow-Up:
- CBC, platelet, q1-3 months x 2 yrs, then q3-6months up to 5yrs
- BM not routinely done, indicated only if peripheral abnormal smear or cytopenias develop.
- Initiate alternative donor search at first relapse

Pharmacology: