Acute Leukemia | AML + ALL

AML | Acute Myeloid Leukemia

- **Epidemiology:** high mortality, generally older patients (>60 y/o)
- **Risk factors:** genetic predisposition, acquired bone marrow diseases, occupational/environmental exposure
- **Secondary AML:** therapy-related AML, often caused by alkylating agents & topo II inhibitors
  - Alkylating agents: cyclophosphamide, melphalan, nitrogen mustards → 4-8 year latency period
  - Topo II inhibitors: etoposide → 1-3 year latency period → more difficult to treat
- **Classification**
  - FAB | French American British: only tell which stage of differentiation is affected
  - WHO | World Health Organization
    - Based on cytogenetics, morphology, and history
    - AML: ≥20% blasts, or less blasts but with poor prognostic cytogenetics
- **Clinical presentation**
  - Constitutional & non-specific: fever, weight loss, anorexia
  - Impaired hematopoiesis (effects on myeloid cell line): anemia, thrombocytopenia, neutropenia
  - **Leukostasis:** WBC > 100K → aggregation & clumping → affects mostly brain & lungs → hypoxemia & hemorrhage
    - Manifestations: headache, blurred vision, MI, dyspnea, transient ischemic attacks, strokes, mental status
    - CNS involvement more common in lymphoblastic leukemias (ALL, CLL)
  - **Tumor lysis syndrome:** ↑breakdown products of dying cancer cells
    - Release of cell contents → ↑LDH, ↑K, ↑Phos, ↑uric acid, ↑SCr, ↓Ca → nephropathy & renal failure
    - Commonly seen in poorly differentiated hematologic disorders: Burkitt's, ALL, AML
    - Risk factors: ↑WBC, ↑blasts, chemo sensitive disease, initiation of therapy
    - Triggers: chemo, steroid treatment, or spontaneous
    - Prevention: allopurinol or rasburicase (↓urate production), IV hydration (↑high urine output)
  - **DIC** | disseminated intravascular coagulation
    - Small blood clots throughout body → small clots consume normal coagulation proteins & platelets → disrupt normal coagulation + normal blood flow to organs → abnormal bleeding + organ damage
    - Seen in M_3 APL or M_5 AML
    - Monitor: fibrinogen, PT/PTT
- **Prognostic factors**

Favorable ☺	Poor ☹
t(15;17), inv(16), t(8;21)	Inv(3), del(5), del(7), t(6;9), t(9;22)
Age<60, good performance status, no MDS or prior malignancy	Age≥60, poor performance status, MDS or prior malignancy, CNS involvement, systemic infection, WBC>100K, CD32 pos, MDR1 overexpression, M6 & M7 FAB subtypes, ↑LDH

- **Diagnosis**
  - Labs: CBC + diff, uric acid, phos, Ca
  - Histology: peripheral blood smear, bone marrow biopsy, aspirate
  - Definitive diagnosis (acute vs. chronic, myeloid vs. lymphoid) needed before treatment
- **Treatment**
  - Curative intent: very aggressive regimens, goal to induce remission, initiate treatment ASAP
  - Two phases: induction & post-remission therapy
    - **Induction therapy**
      - Goal: induce a complete remission by eradicating clone & restoring normal hematopoiesis
      - Bone marrow is assessed 14 days after induction therapy
      - Complete remission criteria: no peripheral leukemia cells, ANC>1K, platelets>100K, bone marrow cellularity>20%, blasts<5%, no extramedullary leukemia
      - **7+3 regimen = Cytarabine + daunorubicin**
        - 7 days of cytarabine continuous infusion: 24hrs/7days @ 100-200 mg/m^2 IVPB
        - 3 days daunorubicin (or any anthracycline) @ 45-90 mg/m^2 IV
        - Doses may be higher for younger patients → better overall survival
        - Complications: tumor lysis syndrome, myelosuppression (surrogate for efficacy)
    - **Post-remission therapy**
      - Goal: eliminate undetectable residual leukemia cells in order to maintain remission

- Poor risk patients: **allogeneic stem cell transplant**
- Intermediate or good risk: HIDAC regimen
    - **HIDAC = high dose cytarabine**
    - Cytarabine 3 g/m^2 q12hr (days 1, 3, 5) for 3-4 cycles
    - Complications

Not seen in cytarabine induction, only in high dose cytarabine regimen

        - *Neurotoxicity & ocular toxicity* ← distributes in TBW (e.g. CNS fluid, tear fluid)
            - Neuro: cerebellar dysfunction e.g. ataxia, nystagmus, dysarthria
            - Ocular: conjunctivitis → prophylaxis with dexamethasone eye drops
        - *Myelosuppression:* anemia, thrombocytopenia, neutropenia
            - Anemia: transfusion if Hgb < 8 g/dL
            - Thrombocytopenia: transfusion if platelets < 10K cells/mm^3
            - Neutropenia (e.g. febrile neutropenia): high risk of infection, need prophylactic po antibiotics if prolonged (<100 cells/mm^3 for >2 weeks), recommend CSF if >55 y/o
        - *Tumor lysis syndrome:* prevent with allopurinol & fluids

- **APL | Acute Promyelocytic Leukemia**
    - **Subtype of AML:** best prognosis, most curable form of AML
    - t(15;17) → accumulation of promyelocytes (immature granulocytes) in bone marrow → ↓normal RBCs & platelets → anemia & thrombocytopenia & ↑bleeding
    - Symptoms & complications: SOB, fatigue, bruising, bleeding, fever, infection, splenomegaly
    - **Fatal complication: DIC**
        - APL results in DIC because the promyelocytes are packed with granules that release tissue factor & activate the coagulation cascade
        - Monitoring parameters: fibrinogen, PT/PTT
    - **Treatment**
        - Without treatment, APL is fatal → treat STAT
        - **Induction: ATRA**
            - ATRA | all trans retinoic acid
            - Vitamin A analog that induces differentiation & maturation of promyelocytes until apoptosis
            - Complications: **retinoic acid syndrome**
                - ↑Cells bursting → cytokine release & capillary leak → cardiogenic & respiratory distress
                - Signs & symptoms: unexplained fever, weight gain, respiratory distress, interstitial pulmonary infiltrates, pleural or pericardial effusions
                - Leukocytosis risk: do not start if WBC > 10K, need cytoreduction first
                - Treatment: discontinue ATRA, start dexamethasone 10mg bid for ≥3 days
        - **Consolidation**: **idarubicin or daunorubicin** for 2 cycles while continuing ATRA
        - **Maintenance:** ATRA + mercaptopurine + MTX
        - **Refractory/relapse:** arsenic
            - MOA: arsenic degrades fusion protein → induces differentiation & apoptosis
            - Indication: induction & consolidation in APL patients refractory/relapsed from ATRA or chemo and with t(15;17), or elderly patients who cannot tolerate ATRA & anthracyclines
            - Toxicities: QT prolongation (monitor EKG), retinoic acid syndrome

ALL | Acute Lymphoblastic Leukemia

- **Epidemiology:** mostly pediatrics (2-5 y/o) or elderly (>50 y/o), but younger patients have more favorable prognosis
- **Risk factors:** chemical exposure, genetic conditions
- **Classification**
    - FAB | French American British
    - WHO | World Health Organization

  Mature B-cell: poor prognosis *Pre-B cell:* intermediate prognosis *Pre-T cell:* good prognosis
- **Clinical manifestations**
    - *Constitutional (non-specific)*: fever, night sweats, weight loss
    - *CNS involvement*: headaches, mental status changes, more common in lymphoid than myeloid leukemias
    - *Pulmonary*: mediastinal mass, pericardial infusions, more common in T cell than B cell ALL
    - *Sanctuary sites affected*: meninges, spinal cord, testes
    - *Lymphoid organs affected*: splenomegaly, hepatomegaly, lymphadenopathy
    - *Leukocytosis*

- **Diagnosis**: bone marrow morphology (e.g. blast %), cytochemical studies, immunophenotyping (CD_)
- **Prognostic factors**
    - Good prognosis: hyperploidy, del(9p)
    - Poor prognosis: Philadelphia chromosome t(9;22), complex karyotype, t(8;14), testicular relapse
- **Treatment**
    - Curative intent, although relapse is common
    - **Treatment:** four phases, very diverse, systemic & local CNS-targeted, for 2-3 years
        - Principles: young adults should be treated with pediatric-type regimens, standard risk patients benefit from allogeneic stem cell transplant
        - **Induction**
            - Intense combo of a variety of chemo drugs with different MOA & toxicity profiles
            - Agents: anthracyclines, vincristine, corticosteroids, HIDAC, HDMTX, peg-asparaginase (peds)
            - Regimens: hyper-CVAD (hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone), Larson regimen, targeted agents (imatinib, rituximab)
                - Hyper-CVAD complications: febrile neutropenia, infection, hepatic/renal dysfunction, infertility, pulmonary fibrosis
                - Pediatric protocol complications: liver fibrosis, secondary malignancies, infertility
                - Tyrosine kinase inhibitors: added as backbone, effective on Philadelphia chromosome
        - **CNS prophylaxis**
            - Administration: lumbar puncture or ommaya reservoir
            - Agents: MTX (± hydrocortisone), cytarabine
            - ↑CNS relapse risk: ↑LDH, ↑proliferative index, ↑WBC
            - Standard chemo does not penetrate CNS
                - Intrathecal admin: MTX, cytarabine, hydrocortisone
                - High dose chemo: MTX, cytarabine
        - **Consolidation/intensification:** similar agents as in induction
        - **Maintenance:** monthly treatment with POMP regimen (6-MP, po MTX, vincristine, prednisone)
        - Poor risk patients: induction + stem cell transplant