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 M3 APL or M5 AML
    - Monitor: fibrinogen, PT/PTT
- **Prognostic factors**

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<th>Favorable ☺</th>
<th>Poor ◻ ◻</th>
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<tr>
<td>t(15;17), inv(16), (t;8;21)</td>
<td>Inv(3), del(5), del(7), t(6;9), t(9;22)</td>
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<td>Age&lt;60, good performance status, no MDS or prior malignancy</td>
<td>Age≥60, poor performance status, MDS or prior malignancy, CNS involvement, systemic infection, WBC&gt;100K, CD32 pos, MDR1 overexpression, M6 &amp; M7 FAB subtypes, ↑LDH</td>
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- **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/m² IVPB
      - 3 days daunorubicin (or any anthracycline) @ 45-90 mg/m² 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
  o **HIDAC = high dose cytarabine**
  o Cytarabine 3 g/m³ q12hr (days 1, 3, 5) for 3-4 cycles
  o Complications
    • **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/mm³
      - Neutropenia (e.g. febrile neutropenia): high risk of infection, need prophylactic po antibiotics if prolonged (<100 cells/mm³ for >2 weeks), recommend CSF if >55 y/o
    • **Tumor lysis syndrome**: prevent with allopurinol & fluids

• **APL | Acute Promyelocytic Leukemia**
  o **Subtype of AML**: best prognosis, most curable form of AML
  o t(15;17) — accumulation of promyelocytes (immature granulocytes) in bone marrow → ↓ normal RBCs & platelets → anemia & thrombocytopenia & ↑ bleeding
  o Symptoms & complications: SOB, fatigue, bruising, bleeding, fever, infection, splenomegaly
  o **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
  o **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