Leukemia, A Review

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Leukemia, a review

Overview

- Acute Myeloid Leukemia (AML)
- Acute Lymphoid Leukemia (ALL)
- Chronic Myeloid Leukemia (CML)
- Chronic Lymphoid Leukemia (CLL)
A Review of Hematopoiesis
Acute Leukemias

**Essentials:**

- Short course of symptoms
- Fatigue, fever, easy bruising, bleeding
- Cytopenias - or pancytopenia
- More than 20% blasts in bone marrow
- Blasts in peripheral blood in 90% cases
Acute Myeloid Leukemia (AML)

- Refers to a group of hematopoietic neoplasms involving cells committed to the myeloid line of cellular development.
- AML is characterized by a clonal proliferation of myeloid precursors with reduced capacity to differentiate into more mature cellular elements.
AML

Incidence:

• 2.3 per 100,000 people per year

• Higher among men than women (2.9 vs 1.9)

• Most common leukemia in adults (80% of cases)

• Vast majority of patients 65 years or older
AML

Etiology:

• Genetic

• Radiation

• Toxic chemical exposure

• Medication (Alkylating-agents, Topoisomerase-II inhibitors, Chloramphenicol, Phenylbutazone, Chloroquine, and Methoxypsoralen)
AML

Most Common Presenting Sx:

• Fatigue (50%)
• Anorexia (30-40%)
• Weight loss (30-40%)
• Fever without evident cause (10%)
• Easy Bruising (5%)
• Bleeding (5%)
AML

Symptoms:

- Nonspecific

- Most related to anemia, leukocytosis, leukopenia, leukocyte dysfunction, or thrombocytopenia

- Symptoms usually present for 3 months or more before diagnosis is made
Other Common Sx:

- Bone pain
- Lymphadenopathy
- Non-specific cough
- Headaches
- Excessive diaphoresis
- Symptoms secondary to mass lesions (granulocytic sarcoma or chloroma)
AML

Physical Findings:

- Fever
- Splenomegaly
- Sternal tenderness
- Multiple bruises
- Bleeding (gingival most common)
- Unexplained infections
- GI bleed
- Pulmonary, intracranial, and retinal hemorrhage
AML

Laboratory and Radiographic Work-up:

• CBC with manual differential
• Uric Acid level-TLS
• Clotting studies (PT, INR, D-dimer, fibrinogen)
• Bone marrow aspirate and biopsy
• Chest xray
• Echo/MUGA
Hematological Findings:

- Anemia (normochromic, normocytic)
- Leukocytosis (median = 15,000)
- Thrombocytopenia (< 100,000)
AML

Morphology and Cytology:

• > 20% myeloblasts in blood and/or bone marrow

• Auer Rods (cytoplasmic granules)

• Positive myeloperoxidase reaction in > 3% blasts
AML Histology
AML

Classification/Subtypes:

• French-American-British Classification
  - Eight major subtypes
  - Based on morphology and cytochemistry

• World Health Organization Classification (W.H.O)
  - Based on molecular, morphologic, and clinical features
  - More commonly used today
WHO classification of myeloid neoplasms

- **Acute myeloid leukemia (AML)**
  - AML w/recurrent cytogenetic translocations- 11%
  - AML w/ myelodysplasia-related features- 6%
  - Therapy-related AML and MDS- 2%
  - AML not otherwise categorized- 81%
AML

Prognostic Factors:

- Age at diagnosis
- Comorbidities (acute vs chronic)
- Chromosomal findings
- Symptomatic interval preceding diagnosis
- Presenting Leukocyte count
- Circulating myeloblast count
- Morphologic characteristics of the leukemic cell
Remission:

• Combination tx with Cytarabine/Idarubicin
• 65-75% will achieve Complete Remission (CR).
• Two-thirds achieve CR after a single cycle. The other one-third after a second course.
• 50% of those who do not achieve CR fail because of a drug-resistant leukemia. The other 50% because of fatal complications of bone marrow or stem cells.
• Those with less favorable cytogenetics and good performance status will likely progress to BMT after CR is achieved.
AML-Treatment

- **Induction chemotherapy**
  - Cytarabine + Idarubicin (7+3 regimen)
    Cytarabine (Ara-C) 100 mg/m²/d civi d1-7
    Idarubicin 12 mg/m²/d iv d1-3

- **Consolidation chemotherapy**
  - HDAC
    Cytarabine (Ara-C) 3 g/m² iv q12h x 6 doses d1, 3 and 5 x 4 cycles
Acute Lymphoid Leukemia (ALL)

- Acute lymphoblastic leukemia (ALL) refers to a group of hematopoietic neoplasms involving cells committed to the lymphoid lineage.
ALL

Incidence

• Approximately 3,000 new cases per year

• Mostly affects children, accounts for 2/3 of childhood leukemia (peak age 4 years)

• Comprises less than 20% of leukemia in young adults

• May be B-cell, T-cell, or null-type (non-B, non-T cell)
ALL

Etiology

• Uncertain, but several proposed linkages:
  · Genetic - Philadelphia chromosome + accounts for approximately 20 to 30 percent of ALL in adults
  · Viral infection (EBV, HIV)
  · Exposure to high energy radiation (T-cell ALL)
  · Toxic chemical exposure
  · Smoking
WHO classification of acute lymphoblastic leukemia

- **Precursor B lymphoblastic leukemia / lymphoblastic lymphoma:**
  - ALL with t(9;22)(q34;q11.2); BCR-ABL (Philadelphia chromosome)
  - ALL with t(v;11q23) (MLL rearranged)
  - ALL with t(1;19)(q23;p13.3); TCF3-PBX1 (E2A-PBX1)
  - ALL with t(12;21)(p13;q22); ETV6-RUNX1 (TEL-AML1)
  - Hyperdiploid > 50
  - Hypodiploid
  - t(5;14)(q31;q32); IL3-IGH

- **Precursor T lymphoblastic leukemia / lymphoma**
Common Sx:

- Pallor
- Fatigue
- Shortness of breath
- Easy bruising
- Petechiae
- Weight loss / failure to thrive
- Bone and/or joint pain
Physical Findings

• Fever
• Splenomegaly and/or hepatomegaly
• Lymphadenopathy
• Multiple bruises
• Petechiae
• Unexplained infections
Laboratory and Radiographic Work-up

- CBC with manual differential
- Chemistry studies to check for organ dysfunction
- Bone marrow aspirate and biopsy
- Genetic/Immunological studies
- Lumbar puncture
ALL

Hematological Findings

• Anemia (normochromic, normocytic)

• WBC < 5,000 (or > 25,000)

• Leukocytosis (median = 15,000)

• Thrombocytopenia (< 50,000)
ALL Histology
ALL Histology
Prognostic Factors:

- Adult vs Childhood type
- Morphology
- Chromosomal findings
- WBC > 50,000
- B-cell type worse than T-cell type
- Lymphadenopathy
- Hepatosplenomegaly
Remission:

- Childhood ALL CR rate is approximately 90-95%
- Adult ALL CR rate is approximately 70-80%
- Patients with poor cytogenetics should progress to BMT
ALL

- **Hyper-CVAD/MTX-Ara-C**

  - **Cycle 1** 3 5 7 (3-4 wks/cycle)
    - Cyclophosphamide (Cytoxan) 300 mg/m2 iv over 2 hrs q12 hrs x 6 doses d1-3
    - Mesna 600 mg/m2/d civi d1-3 to start 1 h before cyclophosphamide till 12 hrs after completion of cyclophosphamide
    - Vincristine 2 mg iv d4, 11
    - Doxorubicin (Adriamycin) 50 mg/m2 iv over 24 hrs d4
    - Dexamethasone (Decadron) 40 mg po qd d1-4 and d11-14

  - **Cycle 2** 4 6 8 (3-4 wks/cycle)
    - Methotrexate (MTX) 200 mg/m2 iv over 2 hrs followed by 800 mg/m2 civi over 22 hrs d1
    - Cytarabine (Ara-C) 3 g/m2 (1 g/m2 for patients over 60 years old) iv over 2 hrs q12 hrs x 4 doses d2-3
    - Leucovorin 50 mg iv q6 hrs starting 12 hrs after completion of MTX till MTX level < 0.05 uM
Intrathecal chemotherapy 

- Prophylaxis 
  - Methotrexate (MTX) 12 mg d2 of each cycle for a total of 3-4 treatments 
  - Cytarabine (Ara-C) 100 mg d8 of each cycle for a total of 3-4 treatments 
- Therapeutic-Intrathecal chemotherapy twice a week 
  - Methotrexate (MTX) 12 mg and Cytarabine (Ara-C) 100 mg respectively) till no more cancer cells in CSF, then decrease intrathecal chemotherapy to once a week x 4, followed by Methotrexate (MTX) 12 mg d2, Cytarabine (Ara-C) 100 mg d8 for the remaining chemotherapy cycles
Acute Leukemia Treatment

Supportive Care:

• Transfusions….
  - Platelets >10,000
  - Hgb >8

• Empiric antibiotic treatment when neutropenic fever present

• Allopurinol for increased uric acid levels due to tumor burden or tumor lysis
Acute Leukemia Treatment

Post-remission Treatment:

• Stem cell transplant

• CNS prophylaxis (ALL)

• Radiation therapy (ALL)

• Prolonged low-dose chemotherapy for 1-3 years (ALL)
Chronic Leukemia

**Essentials:**

- Most are asymptomatic at presentation
- Strikingly elevated WBC
- Marked left-shift
- Philadelphia chromosome
- Splenomegaly typical
- Lymphocytosis
Chronic Myeloid Leukemia (CML)

**Incidence:**

- 1.3 per 100,000 people per year
- Higher among men than women (1.7 vs 1.0)
- Vast majority of patients 40 years or older
- There is no clear etiology
CML

Pathophysiology:

• Philadelphia chromosome (9:22) in up to 95%

• BCR-ABL protein junction
CML

Common Sx:

Note: approximately 70% of patients are asymptomatic at the time of diagnosis

- Lethargy
- Weight loss
- Increasing abdominal girth
- Easy bruising or bleeding
- Excessive diaphoresis
CML

Physical Findings:

- Fever
- Splenomegaly and hepatomegaly
- Bruising
- Bleeding (gingivae most common)
Laboratory and Radiographic Work-up:

- CBC with manual differential
- Serum Vitamin B12 and B12 binding capacity
- Leukocyte alkaline phosphatase (decreased)
- Uric acid level
- Chromosomal testing - Philadelphia chromosome
- Bone marrow biopsy
CML

Hematological Findings:

• Anemia (normochromic, normocytic)

• Leukocytosis (median = 20,000)

• Basophilia

• Thrombocytopenia (< 100,000)
CML Histology
CML Histology
CML

Three Phases:

- **Chronic phase:** 3-5 years. Current treatment is with Tyrosine Kinase Inhibitors (TKIs). BMT is reserved for patients with refractory or progressive disease.

- **Accelerated phase:** New nonrandom cytogenetic abnormalities in up to 80% of patients. Difficult to control. Development of myelofibrosis. Elevated leukocyte counts. Lasts several months before becoming blastic.

- **Blast phase:** > 30% blasts in blood or marrow. Treatment with chemotherapy similar to acute leukemia. Some patients go into remission with treatment, but it is short lived.
CML

Prognostic Factors:

• Age at diagnosis
• Splenomegaly
• Blasts > 5% in blood or marrow at diagnosis
• Basophilia > 7%
• Platelets > 700,000
CML Treatment

- CML therapy is based on phase
  - Chronic: TKIs
  - Accelerated: 2nd generation TKIs, goal is to push back into chronic phase and then proceed with BMT
  - Blast: same as for AML, with combination chemotherapy
Chronic Lymphoid Leukemia (CLL)

**Incidence:**

- 2 new cases per 100,000 people per year
- Comprises 30% of all cases of leukemia
- Most common lymphoid leukemia
- Almost exclusively due to B-cell clonal expansion
- More common in men
- Most common in individuals < 50 years
Etiology:

- Uncertain, several proposed linkages:
  - Genetic
  - Viral infection \((EBV, HIV)\) - Burkitt’s
  - Exposure to high energy radiation (T-cell ALL)
  - Toxic chemical exposure
  - Smoking
Common Sx:
Note: approximately 70% of patients are asymptomatic at the time of diagnosis

- Fever
- Pallor
- Fatigue
- Shortness of breath
- Easy bruising
- Gingival bleeding
- Weight loss
- Frequent infections
Physical Findings:

- Fever
- Splenomegaly and/or hepatomegaly
- Lymphadenopathy
- Multiple bruises
- Bleeding gingivae
- Unexplained infections
Laboratory and Radiographic Work-up:

• CBC with manual differential
• Peripheral smear
• Flow cytometry
• Chemistry studies to check for organ dysfunction
• Lymph node biopsy
Hematological Findings:

- Increased number of lymphocytes on smear
  - smudge cells
- B-cells with CD 19 and CD 5 on flow cytometry
- Small lymphocytic lymphoma present in histology of nodal biopsy
CLL Histology
CLL Histology

Lymphocytes

Smudge Cell
Rai Stage 0 (low risk) lymphocytosis, (> 15,000).

Rai Stage I (intermediate risk) lymphocytosis plus lymphadenopathy.

Rai Stage II (intermediate risk) lymphocytosis plus hepatomegaly or splenomegaly, with or without lymphadenopathy.

Rai Stage III (high-risk) lymphocytosis plus anemia, a hemoglobin < 11 g/dL, with or without lymphadenopathy, hepatomegaly, or splenomegaly.

Rai Stage IV (high-risk) lymphocytosis plus thrombocytopenia(< 100).
CLL

Prognostic Factors:

• Based on RAI classification
• Lymphocytosis
• Lymphadenopathy
• Splenomegaly or Hepatomegaly
• Anemia
• Thrombocytopenia
CLL Treatment

- CLL therapy is based on RAI stage
  - stage 0: Often followed without specific treatment
  - stage I and II: Treatment if symptomatic. Single agent treatment with fludarabine. Combination treatment with CVP or CHOP regimens
  - stage III and IV: Fludarabine, CVP, or CHOP regimens
  - Young patients with this disease are also candidates for bone marrow transplantation
CLL

Remission:

- Remission has not been achieved in CLL.
- Treatment with chemotherapy (fludarabine, CHOP, or CVP) increases median survival rates:
  - Stage 0-I: 10-15 years
  - Stage II-IV: approximately 2-5 years for 90% of patients