Acute Myelogenous Leukemia: FOCUS on Acute Promyelocytic Leukemia (APL)

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Disclosures

☐ Sara Tinsley-Vance is on the speaker's bureau for Astellas; consultant for Novartis; consultant and on the speaker's bureau for Bristol Myers Squibb, Incyte, Jazz, CTi

☐ Relevant financial relationships have been mitigated
Objectives

- Review epidemiology, etiology, pathophysiology of AML
- Identify risk categories of AML according to European Leukemia Net
- Discuss clinical presentation of AML
- Recognize the latest updates in management of acute promyelocytic leukemia (APL)
- Outline critical aspects of treatment for induction of APL
Leukemia

- Group of hematologic malignancies affecting the bone marrow and lymphatic system
- 1847 German pathologist Virchow "leukemia" or white blood
- Abnormalities of proliferation of lymphoid and myeloid cell lines
- Acute versus chronic
Epidemiology for Acute Myelogenous Leukemia (AML)

- 20,380 new cases projected
- 11,310 deaths projected
- Slightly more men than women diagnosed
- Median age at diagnosis of 69 years
- 5-year relative survival rate of ~ 30%

Epidemiology for Acute Promyelocytic Leukemia

- Makes up between 7-8% of adult AML cases
- Median age at diagnosis of 47 years
- Slightly more men than women
- Rarely diagnosed prior to the age of 20
- Survival rates > 90%
- More common among Hispanics
Etiology | Genetic Factors

- Evidence of familial clustering
- Genetic disorders
  - Down's syndrome
  - Bloom's syndrome
  - Fanconi's anemia
  - Klinefelter's syndrome
- Acquired chromosomal abnormalities
  - 55-78% of adult patients with acute leukemia
- Most commonly evolve from MDS

Etiology-Chemicals

- Alkylators
- Antibiotics
  - Chloramphenicol
  - Phenylbutazone
- Chemotherapy
  - Etoposide
  - Topoisomerase II inhibitors
- Therapy related leukemia is 20-25%

Etiology - Radiation

- Most conclusively identified leukemogenic factor in humans
  - Japanese survivors of atomic bomb
  - Early radiologists

Etiology

- Most often, the cause of acute myelogenous leukemia is unknown
- Older age
- Germline mutations

Pathophysiology

- Normal regulatory mechanisms for cell proliferation and maturation are missing or abnormal.
  - Arrest of the cell in an early phase of maturation causes accumulation of immature cells
  - Abnormal proliferation of these immature cells
  - Crowding of other marrow elements
- Driven by germline and acquired somatic mutation
Clinical Manifestations

- Neutropenia
  - Fever
  - Abdominal pain
  - Respiratory infection
  - Perirectal abscess
  - Adenopathy

Clinical Manifestations

- Neutropenia
  - Mucositis
- Fungal invasions with prolonged neutropenia

Clinical Manifestations

- Anemia
  - Fatigue or malaise
  - Pallor
  - Dyspnea
Clinical Manifestations

- Leukemic infiltrates
  - Pain or swelling in bones and joints
  - Hepatomegaly
  - Splenomegaly

Clinical Manifestations

- **Thrombocytopenia**
  - Purpura, petechiae, ecchymoses
  - Bleeding gums
  - Epistaxis
  - Retinal hemorrhage
  - Intracranial bleeding

Assessment of Acute Leukemia

- Physical symptoms and findings influenced by:
  - Type of leukemia cell
  - Degree of leukemic cell burden
  - Involvement of organs and systems outside the bone marrow or circulation
  - Depression of normal marrow elements by leukemic process

Clues from Patient History

- Signs and symptoms normally present for less than three months
- Most complaints are nonspecific
  - Common symptoms include fatigue, weight loss, infections, unexplained bleeding, bone pain, and shortness of breath

Diagnostic studies for AML

- AML versus ALL
  - Suggested by peripheral smear
  - Bone marrow biopsy and aspiration
    - Normally hypercellular
    - Auer rods diagnostic of AML
  - 90% have blast cells present in the peripheral blood work

Diagnostic studies

- Cytogenetic analysis
  - Confirm diagnosis
  - More than 2/3 of patients have nonrandom chromosomal abnormalities
  - Translocations, inversions, or loss or gain in chromosome number
  - Prognostic indicators

Diagnostic Studies - Flow cytometry

- Immunologic studies
  - Clusters of differentiation
    - Reside on surface of hematopoietic cells
  - Assist with distinguishing between AML and ALL
  - Some patients have markers for both lymphoid and myeloid leukemia or leukemia of ambiguous lineage (21%)

Diagnostic Studies: Fluorescence In Situ Hybridization (FISH)

- Used for detecting cytogenetic abnormalities
- Useful when metaphases are not available from traditional karyotyping
- Must identify what you are "FISHing" for from the specimen

Diagnostic Studies: Reverse Transcriptase Polymerase Chain Reaction (PCR)

- High specificity and sensitivity
- Used to measure minimal residual disease in certain subtypes of AML, including APL
  - PML-RARA
  - BCR/ABL
  - RUNX1

Three Risk Categories

Based on Genetic and molecular Abnormalities

Guides Treatment recommendations

Emergency Management of APL

- Individuals with suspected APL should be **immediately hospitalized** and managed as a medical emergency.

- Even before confirmation:
  - ATRA
  - Measures to counteract the **coagulopathy** should be initiated immediately.
    - Based solely on the clinical suspicion of APL
    - Review of the peripheral blood (PB) smear

Latest Updates in Management of APL

- Diagnosis should be confirmed by molecular detection of PML-RARA fusion (or rare molecular variants)
  - PCR for PML/RARA
  - FISH for PML/RARA (quicker turn around time)

- Management of coagulopathy
  - Treatment with ATRA should be started immediately
  - Transfusions of fibrinogen and/or cryoprecipitate, platelets, and fresh-frozen plasma should be given immediately
  - And daily or more than once a day if needed, to maintain the fibrinogen concentration above 100–150 mg/dL, the platelet count above $30 \times 10^9$/L to $50 \times 10^9$/L, and the INR below 1.5

Latest Updates in Management of APL

- Monitor at least **daily** and more frequently if required, until all clinical and laboratory signs of the coagulopathy disappear
  - Platelet counts
  - Routine coagulation parameters
    - Prothrombin time
    - Activated partial thromboplastin time
    - Thrombin time
    - Fibrinogen
    - Fibrinogen-fibrin degradation products

Latest Updates in Management of APL

- Recommend avoiding the following during remission induction
  - Central venous catheterization (except PICC)
  - Lumbar puncture
  - Other invasive procedures (eg, bronchoscopy) due to high risk of hemorrhagic complications

- Determine clinical risk versus benefit of hemorrhagic events

Treatment options

- Non–high-risk patients (WBC count ≤10 × 10⁹/L)
  - ATRA plus ATO for induction (daily until complete remission [CR] or for a maximum of 60 days)
  - Consolidation therapy (ATO 5 days per week, 4 weeks on 4 weeks off, for a total of 4 courses and ATRA 2 weeks on and 2 weeks off for a total of 7 courses)
  - EKG at the beginning of each treatment week to monitor for QTc prolongation
  - Keep magnesium at 2.0 and potassium at 4.0
  - Monitor medication lists carefully and avoid other QTc prolonging medications
  - Such as certain antiemetics and antifungals
Treatment options

- Non-high-risk patients (WBC count ≤10 × 10⁹/L)
  - ATRA plus ATO was associated with:
    - Significantly less myelosuppression
    - Fewer infections
  - More frequent increases in:
    - Liver enzymes
    - QTc prolongation
    - Reversible and manageable with temporary drug discontinuation
    - Dose adjustment is sometimes necessary
Treatment options

- For high-risk APL patients (WBC count >10 × 10⁹/L)
  - ATRA plus ATO with the addition of some cyto-reductive chemotherapy
    - A single dose of GO (6 mg/m²)
  - ATRA plus chemotherapy
    - 90% to 95% CR rates
    - 85% to 90% rates of long-term survival
    - ATRA plus daunorubicin and cytarabine
    - ATRA plus idarubicin alone
    - Consolidation therapy should entail administration of at least 2, and possibly 3, further cycles of ATRA plus anthracycline–containing chemotherapy.

Thank you for your attention!