Leukemia and Myelodysplastic Syndromes

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Diagnostic Evaluation of Blood Disorders

- History & Physical
- Labs: CBC with differential, coagulation studies, chemistries, uric acid and LD
- Peripheral blood smear
- Bone marrow aspiration and biopsy with cytogenetics and immunophenotyping
- Chest X-ray
- CSF sampling if symptomatic

Bone Marrow Aspirate and Biopsy

- **Aspirate**: enumerates individual marrow cell types and detects cytologic abnormalities
- **Biopsy**: examines the architecture of the marrow, especially aggregates and fibrosis
Flow Cytometry

- Measurement of cellular properties as they move in a stream past a detector which allows cells to be sorted
- Establishes lineage markers, state of maturation or differentiation
- Qualitative and quantitative analysis of cells
- Used to monitor reconstitution of immune system

Immunophenotyping

- Uses fluorochrome-tagged monoclonal antibodies
- Antibodies are used to detect specific antigens (markers) that are expressed on cells

Cytogenetics

- Looks at gene translocations, inversions and rearrangements.
- Look at chromosome banding and abnormalities in Fluorescent In Situ Hybridization (FISH)
- Useful to monitor minimal residual disease

### Common Markers in Leukemias

<table>
<thead>
<tr>
<th>Name</th>
<th>Normal Cell Expression</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4</td>
<td>T cells</td>
<td>Mature T cell neoplasms and AML</td>
</tr>
<tr>
<td>CD8</td>
<td>T cells and NK cells</td>
<td>Mature T cell neoplasms</td>
</tr>
<tr>
<td>CD9</td>
<td>Precursor B, activated T</td>
<td>Precursor B cell ALL</td>
</tr>
<tr>
<td>CD11b</td>
<td>Maturing neutrophils and some lymphoid</td>
<td>AML and MDS</td>
</tr>
<tr>
<td>CD13</td>
<td>Myeloid and monocytic</td>
<td>Myeloid neoplasms</td>
</tr>
<tr>
<td>CD15</td>
<td>Myeloid and monocytic</td>
<td>AML, MDS</td>
</tr>
<tr>
<td>CD19, 20</td>
<td>B cells</td>
<td>ALL B cell lineage</td>
</tr>
<tr>
<td>CD33</td>
<td>Myeloid and monocytic</td>
<td>AML, MDS</td>
</tr>
<tr>
<td>CD34</td>
<td>HPC, B and T precursor</td>
<td>AML and ALL</td>
</tr>
<tr>
<td>CD38</td>
<td>Precursor B, T, myeloid</td>
<td>CLL</td>
</tr>
<tr>
<td>CD43</td>
<td>T, myeloid and some B</td>
<td>CLL</td>
</tr>
<tr>
<td>CD45</td>
<td>B and T</td>
<td>Distinguishes btw precursor and mature neoplasm</td>
</tr>
<tr>
<td>CD58</td>
<td>Leukocytes</td>
<td>Distinguishes ALL from other B cell</td>
</tr>
<tr>
<td>HLA-DR</td>
<td>Myeloblasts, monocytes, B, T</td>
<td>APL, AML, MDS</td>
</tr>
</tbody>
</table>
Presenting Signs and Symptoms

- None
- Pancytopenia
- WBC elevation
- Pallor
- Petechiae
- Bleeding
- Easy bruising

- Nonspecific fatigue
- Weakness
- Fever
- Persistent infection
- Bone/joint pain
- Weight loss
- Night Sweats

Myelodysplastic Syndromes (MDS)

- A group of diseases of the blood and bone marrow
- More common in the elderly and male
- 12,000 cases per year (3.3/100,000)
- Primary (de novo) or Secondary (treatment related)
- Known risk factors
  - Age
  - Smoking
  - Benzene, solvents and agriculture chemicals
  - Chemo and radio therapy for other cancers

MDS: Diagnosis

- Exam
- Blood tests
  - Anemia – low iron, folate, or B12 or other condition that might breakdown red blood cells
- Blasts >5% of marrow cells
- Cytogenetic abnormalities
  - Y abnormalities of chromosome 5 or 7
  - Deletion 5q, 17p or 20q
  - 11q23
  - Trisomy 8

MDS: Prognosis

- Favorable
  - Low amount of cytopenias
    - ANC <1800
    - Platelets <100K
    - Hgb <10g/dL
  - Blasts in marrow (<10%)
  - Cytogenetics
    - Del 5q alone
    - Del 20q alone
    - Y related abnormality
Leukemia

- A cancer of the blood, including the bone marrow and lymphatic system.
- Begins with the mutation, then production of dysfunctional white blood cells by the bone marrow.
- 2015: 54,270 diagnoses with 24,450 deaths.
- 3% of all diagnoses and 4% of all deaths

<table>
<thead>
<tr>
<th></th>
<th>AML</th>
<th>CML</th>
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<tbody>
<tr>
<td></td>
<td>20,830 cases</td>
<td>6660 cases</td>
</tr>
<tr>
<td></td>
<td>10,460 deaths</td>
<td>1140 deaths</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>ALL</th>
<th>CLL</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>6250 cases</td>
<td>14,620 cases</td>
</tr>
<tr>
<td></td>
<td>1,450 deaths</td>
<td>4,850 deaths</td>
</tr>
</tbody>
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Chronic Leukemias

Slow accumulation of malignant myeloid or lymphocytic cells. Slow growth = longer survival time.

Chronic Myelogenous Leukemia (CML)

- Risk Factor
  - Radiation
- Unknown
- Disease of the older adult, rarely diagnosed in children
CML: Pathophysiology

- Philadelphia chromosome (t9;22)
  - The translocation creates a fusion protein called Bcr-Abl
  - Abl protein involved in growth, differentiation and programmed cell death
  - Combining with Bcr protein causes continuous activation without normal apoptosis
- Results in proliferation of WBCs, RBCs, and platelets

Philadelphia Chromosome

This chromosomal abnormality is so named because it was first discovered and described in 1960 by two scientists from Philadelphia: Peter Nowell and David Hungerford.

CML: Classification

<table>
<thead>
<tr>
<th>Phase</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic</td>
<td>Elevated WBCs, normal bone marrow function, Philadelphia chromosome +, Bcr-Abl fusion protein present</td>
</tr>
<tr>
<td>Accelerated</td>
<td>10-15% blasts in blood or bone marrow, 20% peripheral blood basophils, abnormal platelet count (↑ or ↓), decrease RBC, increasing genetic abnormalities, increasing spleen size</td>
</tr>
<tr>
<td>Blastic</td>
<td>&gt;30% blasts in bone marrow</td>
</tr>
<tr>
<td>Myeloid</td>
<td>75% of patients</td>
</tr>
<tr>
<td>Lymphoid</td>
<td>25% of patients</td>
</tr>
<tr>
<td>Extramedullary blasts</td>
<td></td>
</tr>
</tbody>
</table>

CML: Presenting Signs and Symptoms

- Increased WBC (average on diagnosis is 150,000), RBC and platelets
  - Splenomegaly (90% of patients)
- Malaise
- Fever
- Night sweats
- Weight loss
- Abdominal fullness
- SOB

*Many patients are asymptomatic and the disease is uncovered with a routine CBC
CML: Prognostic Factors

• Unfavorable
  – Accelerated phase or blast phase
  – Enlarged spleen
  – Bone damage due to growth of leukemia
  – Increased basophils and eosinophils
  – Very high or very low platelet counts
  – Age ≥ 60 years
  – Multiple chromosome changes
  – Poor performance status

CML: Treatment Options

• Targeted Therapies
  • Tyrosine Kinase Inhibitors (TKI)
    • Imatinib
    • Sorafenib
  • BMT
  • Clinical trial

• Other treatments
  • Hydroxyurea
  • Interferons

  • Used prior to Targeted Therapies discovery and may be used in conjunction

CML: Side Effects of Targeted Therapies*

• Myelosuppression
• Nausea
• Edema (especially periorbital)
• Fatigue
• Athralgias and Myalgias
• Diarrhea
• Skin rashes
• QT prolongation

*Only 2% of patients discontinue the drug because of side effects

CML: Supportive Care

• Leukocytosis: hydroxyurea, leukapheresis, imatinib
• Thrombocytosis: hydroxyurea, apheresis, antiaggregants, anagrelide
CML: Ongoing Monitoring

- Responding to treatment:
  - Bcr-Abl levels measured every 3 months
  - Bone marrow cytogenetics every year
- Complete cytogenetic response
  - Bcr-Abl levels measured every 3 months
  - Bone marrow cytogenetics every 12-18 months
- If Bcr-Abl transcript levels begin to rise, recheck monthly

CML: Treatment of Advanced Disease

- Accelerated Phase
  - TKI therapy
  - BMT
  - Clinical Trial
- Blast Crisis
  - Lymphoid
    - TKI, then BMT
    - ALL-type induction, then BMT
    - Clinical trial
  - Myeloid
    - TKI, then BMT
    - Clinical trial
    - AML-type induction therapy and then BMT

CLL: Etiology

- Slow growing: greater than normal production of developed cells
- Unknown
- Risk Factors
  - Herbicides used in Vietnam
  - Family history of CLL or any B-cell malignancy
    - Small risk
- Disease of the older adult

CLL: Pathophysiology

- B cells undergo malignant transformation
  - Initial accumulation in the bone marrow
  - Spread to lymph nodes and lymphoid tissues
  - Eventual splenomegaly and hepatomegaly.
- Anemia, neutropenia, thrombocytopenia, and decreased immunoglobulin levels
- Develop hypogammaglobulinemia and impaired antibody response
CLL: Presenting Signs and Symptoms*

- Painless lymphadenopathy
- Splenomegaly
- Hepatomegaly
- Elevated WBCs (majority are small, mature lymphocytes)
- Small lymphocytes in bone marrow
- Hypogammaglobulinemia
- "B" symptoms
  - Fever
  - Fatigue
  - Night sweats
  - Unexplained weight loss

*25% of patients are asymptomatic at presentation

CLL: Diagnostic Evaluation (in addition to previous workup)

- H & P
  - (Presence or absence of B symptoms)
- Quantitative immunoglobulins
- Chest/abdominal/pelvic CT
  - (especially if peripheral adenopathy absent)
- Beta-2 microglobulin levels

CLL: Classification

- Two systems for classification exist, the Rai and Binet systems (Rai more accepted):

<table>
<thead>
<tr>
<th>CLL Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal</td>
</tr>
<tr>
<td>I</td>
<td>Stage 0 plus enlarged lymph nodes</td>
</tr>
<tr>
<td>II</td>
<td>Stage 0 plus enlarged spleen or liver</td>
</tr>
<tr>
<td>III</td>
<td>Stage 0-11 plus hemoglobin &lt;11</td>
</tr>
<tr>
<td>IV</td>
<td>Stage 0 plus platelets &lt;100K</td>
</tr>
</tbody>
</table>

CLL: Prognostic Factors

- Stage
  - Low risk disease (Rai O or Binet A) has a 10-12 year median survival
  - High risk disease (Rai IV or Binet C) has a 1-3 year median survival

- Other unfavorable factors
  - Lymphocyte doubling time <1 year
  - Low hemoglobin
  - Diffuse BM involvement
  - Elevated beta-2 microglobulin levels
  - Chromosomal abnormalities
    - Most unfavorable with exception of Deletion chromosome 13
CLL: Therapy

- No current cure for CLL
- "Watch and Wait"
- BMT
- Goals are:
  - Slow growth
  - Provide long periods of remission
  - Improve quality of life

Indications for treatment:
- Rapid increase in lymphocyte counts
- Enlarged lymph nodes
- Enlarged spleen
- Rai III or IV stage
- Cytopenias
- Recurrent infection
- Threatened end-organ function
- Bulky disease
- Steady progression
- Histologic transformation

Chemotherapy or Targeted therapies

Other therapies
- Blood cell growth factors
- Radiation therapy
- Splenectomy

CLL Therapy: Supportive Care

- Infection prophylaxis
- IVIg for patients with hypogammaglobulinemia

CLL: Ongoing Monitoring

- CBC
- H & P every 3-6 months for “watch and wait” patients
**CLL: Treatment of Relapse or Disease Progression**

- Targeted therapies
- Allogeneic BMT
- Clinical trial

**AML: Etiology**

- Risk Factors
  - Congenital disorders: Down’s syndrome, Fanconi’s anemia, Bloom’s syndrome
  - Preceding bone marrow disease: Myelodysplasia, Myeloproliferative disorder, Aplastic Anemia
  - High doses of radiation
  - Benzene
  - Cigarette smoke
  - Prior chemotherapy: Alkylating agents, anthracyclines, epipodophyllotoxins
  - Family history, especially identical twin

**AML: Presenting Signs and Symptoms**

- Pancytopenia
- WBC elevation
- Pallor
- Petechiae
- Ecchymosis
- Retinal hemorrhages
- Gingival hypertrophy
- Cutaneous lesions
- Chloroma
- Bleeding
- Easy bruising
- Nonspecific fatigue
- Weakness
- Fever
- Persistent infection
- Bone/joint pain
- Weight loss

**AML: Classification**

- Two systems
  - World Health Organization (WHO) divides AML into 4 subtypes, based on prognosis
  - French-American-British (FAB) divides AML into 8 subtypes based on precursor cell from which the leukemia developed
- May see either or both systems
AML: WHO Classification

- AML with recurrent genetic abnormalities
- AML with multilineage dysplasia
- AML and MDS, therapy-related
- AML not otherwise categorized (then go to FAB classification)

- Blast threshold of 20% or any blasts with recurrent genetic abnormalities

AML: FAB Classification

- M0 (undifferentiated AML)
- M1 (myeloblastic, without maturation)
- M2 (myeloblastic, with maturation)
- M3 (promyelocytic), or acute promyelocytic leukemia (APML)
- M4 (myelomonocytic)
- M5 (monoblastic leukemia (M5a) or monocytic leukemia (M5b))
- M6 (erythrocytic)
- M7 (megakaryoblastic)

- Blast threshold 20%

AML: Prognostic Factors

- Favorable
  - Younger age
  - Lower WBC at presentation
  - Auer rods present
  - Lower percentage of blasts in BM
  - De novo presentation
  - Cytogenetics
  - Good performance status
  - APML

AML: Before Therapy

- HLA typing of patient (potential BMT)
- MUGA scan or echocardiogram (if concerned about cardiac function)
- WBC Depletion
  - Leukapheresis
  - Hydroxyurea
  - Allopurinol
  - Rasburicase
- Central venous catheter placement
  - Necessary for long term but not for starting therapy
  - External catheter preferred over implanted port.
### AML: Therapy

- **Induction**
  - Initial treatment
- **Standard chemotherapy or clinical trial**
- If blasts reappear during count recovery, proceed with 2nd induction
- **Consolidation**
  - Strengthen the remission
  - Consists of chemotherapy and/or BMT
- **Monitoring**
  - CBC 2-3 times/week
  - BMA: CBC abnormal or failure to recover counts

### Side effects of AML Therapy

- **Induction**
  - Pancytopenia
  - Tumor Lysis Syndrome (TLS)
  - Mucositis
  - Diarrhea
  - Alopecia
- **Consolidation**
  - Hand-Foot syndrome
  - Cerebellar toxicity
  - Ocular toxicity
- **Longer Term**
  - Cardiac toxicity (CHF)

### AML Therapy: Supportive Care

- Antibiotics, antivirals, antifungals
- Growth factors
- Blood products
- Tumor Lysis prophylaxis
- Pain management
- Anti-diarrheals

### AML: Ongoing Monitoring

- CBC every 1-3 months for 2 years, then every 3-6 months up to 5 years
- BM aspirate only if CBC or peripheral smear abnormal
- Initiate donor search (related or unrelated) for BMT at first relapse or with poor risk cytogenetics
AML: Treatment of Relapse

• Age <60
  – Early
    • Clinical trial
    • Salvage chemo then BMT
  – Late (>6 months)
    • Clinical trial
    • Salvage chemo followed by BMT
    • Repeat induction

• Age >60
  – Early
    • Clinical trial
    • Palliative Care
  – Late (>6 months)
    • Clinical trial
    • Repeat induction
    • Palliative Care

A special kind of AML: Acute Promyelocytic Leukemia (APML)

• Subtype of AML (M3)
• About 10% of all AML cases
• Patients younger with a median age of 40.
• Often presents with Disseminated Intravascular Coagulation (DIC)

APML
Special Considerations

• Coagulopathies require aggressive blood component therapy

• Therapy:
  – Consists of agents that encourage growth of promyelocytes into mature granulocytes

ALL: Pathophysiology

• Leukemic blasts may be present at the time of diagnosis in the bone marrow, thymus, liver, spleen, lymph nodes, testes, and CNS.
ALL: Etiology

- Risk factors include
  - Radiation
    - Electromagnetic fields
  - Exposure to
    - Diesel, gasoline
    - Pesticides
    - Smoking
  - Inherited Genetic syndromes
    - Down or Bloom Syndrome
    - Largely Unknown

ALL: Presenting Signs and Symptoms

- Lymphadenopathy
- Hepatosplenomegaly
- Pancytopenia
- WBC elevation
- Pallor
- Petechiae
- Ecchymosis
- Retinal hemorrhages
- Gingival hypertrophy
- Cutaneous involvement
- Headache
- CNS changes
- Mediastinal mass
- Bleeding
- Easy bruising
- Fatigue
- Weakness
- Fever
- Persistent infection
- Bone pain
- Weight loss
- Dyspnea

ALL: Classification

- Two systems
  - World Health Organization (WHO) divides ALL into 3 subtypes, based on immunophenotype
  - French-American-British (FAB) divides ALL into 3 subtypes, based on cellular morphology

ALL: WHO Classification

- Precursor B-cell
  - 4 subtypes based on cytogenetics
- Precursor T-cell
- Burkitt cell leukemia
ALL: Prognostic Factors

• Favorable
  – Absence of t(9;22) [Philadelphia chromosome] or t(4;11)
  – Age <30
  – WBCs <30,000 (B-cell) or <100,000 (T cell) at presentation
  – Rapidity of induction remission

ALL: Before Therapy

• Lumbar puncture
• HLA typing of patient (potential BMT)
• MUGA scan (if concerned about cardiac function)
• WBC depletion (less common than in AML)
  – Leukapheresis
  – Hydroxyurea
• Central venous catheter placement
  – Implanted port

ALL: Therapy

• Four phases
  – Induction
    • Multiple agents (IV and PO) over one month
    • Use chemotherapy and targeted agents
  – CNS Prophylaxis
  – Consolidation
    • Multiple agents (IV and PO)
    • Varied in number of cycles given (1-10)
  – Maintenance
    • 2 years in adults
    • 2-3 years in children

ALL: CNS Prophylaxis

• Without CNS prophylaxis, 35% will experience CNS disease
• With CNS prophylaxis, 10% of patients will experience CNS disease

IT chemotherapy is given either via LP or an Ommaya reservoir
Side effects of ALL Therapy

- Pancytopenia
- Tumor Lysis Syndrome
- Pancreatitis
- Mucositis
- Constipation
- Alopecia
- Peripheral neuropathy
- Steroid induced diabetes, psychosis
- Avascular necrosis (long-term)

ALL Therapy: Supportive Care

- Antibiotics, antivirals, antifungals
- Growth factors
- Blood products
- TLS prophylaxis
- Bowel program
- Pain management
- Antiemetics

ALL: Ongoing Monitoring

- Routine CBC during therapy
- After completion of therapy: Assessment every 3-6 months for 2 years, then every 6-12 months for 3 years
  - H&P
  - CBC
  - Bone marrow aspirate if indicated

ALL: Therapy for Relapse

- Salvage Chemotherapy
  - Agents not used previously
- BMT
- Clinical trial

Recurrent ALL has a 1-year survival rate of 24% and a 5-year survival rate of 3%
Common Nursing Concerns in Leukemia

- Neutropenia
- Anemia
- Thrombocytopenia
- Mucositis
- Disseminated Intravascular Coagulation
- Tumor Lysis Syndrome
- Nausea/vomiting
- Diarrhea/constipation
- CNS alterations
- Depression
- Existential distress

See article, Assessing Adults with Leukemia, by Murphy-Ende and Chemecy for medical and nursing interventions for these common problems.

Patient Resources

- Leukemia and Lymphoma Society
  - www.leukemia.org
- American Cancer Society
  - www.cancer.org
- BMT Infonet
  - www.bmtinfonet.org
- National Comprehensive Cancer Network
  - www.nccn.org
- National Marrow Donor Program
  - www.marrow.org
- Fertile Hope
  - www.fertilehope.org