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 (as needed)
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 (E.g. CD20, CD33, CD45, CD54).

Cytogenetics

- Looks at gene translocations, inversions and rearrangements.
- Look at *chromosome* banding and abnormalities in Fluorescent In Situ Hybridization (FISH).
- Used to identify and monitor 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

- Pancytopenia
- WBC elevation
- Pallor
- Petechiae
- Bleeding
- Easy bruising
- Nonspecific fatigue
- Weakness
- Fever
- Persistent infection
- Bone/joint pain
- Weight loss
- Night Sweats

And...NONE!

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 radiation therapy for other cancers

MDS: Diagnosis

- Exam
- Blood tests
  - Anemia – low iron, folate, or B12
  - 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 or 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>Diagnosis</td>
<td>20,830 cases</td>
<td>6660 cases</td>
</tr>
<tr>
<td>Deaths</td>
<td>10,460</td>
<td>1140</td>
</tr>
</tbody>
</table>

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

CML: Etiology

- Risk Factor
  - Radiation exposure
  - Unknown
- Disease of the older adult, rarely diagnosed in children

Chronic Leukemias

Slow accumulation of malignant myeloid or lymphocytic cells.
Slow growth = longer survival time.
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
    - No brakes in differentiation or cell growth, only gas pedal

- Results in proliferation of WBCs, RBCs, and platelets

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, abnormal platelet count (↑ or ↓), decrease RBC, increasing spleen size</td>
</tr>
</tbody>
</table>
| Blastic   | >30% blasts in bone marrow
           | Myeloid
           | 75% of patients
           | Lymphoid
           | 25% of patients
           | Extramedullary blasts (present in tissues) |

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

CML: Side Effects of Targeted Therapies

- Myelosuppression
- Nausea
- Edema (especially periorbital)
- Fatigue
- Arthralgias 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
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

- Research to standard of care: no detectable disease, discontinue therapy and monitor for return of disease

CML: Treatment of Advanced Disease

- Accelerated Phase
  - TKI therapy
  - BMT
  - Clinical Trial

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

CML Case Study

- 42 yo female presented to PMD with one month history of headache and flu-like symptoms. Fever to 101° over past 2 days.
- WBC 109K, hct 10.6, plt 271K. 38% blasts in peripheral blood.
- Lumbar puncture revealed 83% blasts.
- Bone marrow showed hypercellular bone marrow, 95% cellularity with 60-70% blasts. Positive BCR/ABL by FISH and 9;22 Translocation. Deletion in 16 with gain in 4 and 8.
- Started on hydroxyurea and IT chemo. Also started on induction chemotherapy with dasatinib.
- Received 6 IT doses before clearing CSF.
- Dasatinib dc’d d due to pancytopenia.

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
- 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.
- Decreased
  - RBC
  - WBC
  - Platelet
  - 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 usual workup)

- H & P: Presence or absence of B symptoms
- Quantitative immunoglobulins
- Chest/abdominal/pelvic CT
- Beta-2 microglobulin levels

CLL: Classification

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

<table>
<thead>
<tr>
<th>Rai</th>
<th>Binet</th>
</tr>
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<tbody>
<tr>
<td>0</td>
<td>Abnormal increase in number of lymphocytes in blood and marrow</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 0-1 plus hemoglobin &lt;11</td>
</tr>
<tr>
<td>IV</td>
<td>Stage 0 plus platelets &lt;100K</td>
</tr>
<tr>
<td>A</td>
<td>Increase in number of lymphocytes and &lt; 3 enlarged lymph node areas</td>
</tr>
<tr>
<td>B</td>
<td>Increase in number of lymphocytes and &gt; 3 enlarged lymph node areas</td>
</tr>
<tr>
<td>C</td>
<td>Same as B and Hemoglobin &lt;10, 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

- **Poor prognostic factors**
  - Lymphocyte doubling time <1 year
  - Low hemoglobin
  - Diffuse BM involvement
  - Elevated beta-2 microglobulin levels
  - Chromosomal abnormalities
    - ZAP-70 present
    - 11q or 17p deletion
    - CD38 elevation
    - Chromosome 13 deletion favorable

**CLL: Therapy**

- **No current cure**
- “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

**CLL Therapy: Supportive Care**

- **Chemotherapy or Targeted therapies**

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

- **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

Acute leukemias

Rapid increase in myeloid or lymphoid cells. Quick growth = short life span

AML: Risk Factors

- Congenital disorders
- Preceding bone marrow disease
- High doses of radiation
- Benzene
- Tobacco
- Prior chemotherapy
- Family history
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 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 (erythroid)
- 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
- Cardiac function: MUGA scan or echocardiogram
- WBC Depletion
  - Leukapheresis
  - Hydroxyurea
- Tumor Lysis syndrome prevention
  - Allopurinol
  - Rasburicase
- Central venous catheter placement
  - Necessary for long term but not for starting therapy
  - External catheter preferred over implanted port.
  - For patients not eligible for BMT, PICC over tunneled catheter is sufficient

AML: Therapy

- Remission Induction
  - Initial treatment
  - May repeat if blasts recur during count recovery
- Standard chemotherapy or clinical trial

- Intensive Consolidation
  - Prevent recurrence
  - Consists of higher doses of chemotherapy and/or BMT
- Monitoring
  - CBC 2-3 times/week
  - BMA: CBC abnormal or failure to recover counts

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 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
  - Exposure to
    - Diesel, gasoline
    - Pesticides
    - Smoking
  - Inherited genetic syndromes
  - 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
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

• HLA typing
• MUGA scan
• WBC depletion
  – Leukapheresis
  – Hydroxyurea
• Neurological exam/LP
• Testicular exam
• Central venous catheter placement
  – Implanted port preferred

ALL: Therapy

• Four phases
  – Remission Induction
  – CNS Prophylaxis
  – Consolidation (Intensification)
  – Maintenance
    – ~2 years dependent on disease subtype and prognostic factors

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
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

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
  • Depression
  • Existential distress
• Tumor Lysis Syndrome
• Nausea/vomiting
• Diarrhea/constipation
• CNS alterations
• Peripheral neuropathies

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)

• Depression
• Existential distress
Side effects of ALL Therapy

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

Supportive Care

- Antibiotics, antivirals, antifungals
- Growth factors
- Blood products
- Tumor Lysis prophylaxis
- Pain management
- Anti-diarrheals (AML treatment)
- Bowel program (ALL treatment)

Patient Resources

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