Leukemia and Myelodysplastic Syndromes

Lenise Taylor, MN, RN, AOCNS, BMTCN
BMT/Immunotherapy CNS
Seattle Cancer Care Alliance/UWMC
ltaylor@seattlecca.org

Diagnostic Evaluation of Blood Disorders

- History & Physical
- Labs: CBC with differential, coagulation studies, chemistries, uric acid and LD
  - Other disease specific blood tests
- 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 monocyte</td>
<td>Myeloid neoplasms</td>
</tr>
<tr>
<td>CD15</td>
<td>Myeloid and monocyte</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 monocyte</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

OR...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

- 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.
- 3% of all diagnoses and 4% of all deaths

<table>
<thead>
<tr>
<th></th>
<th>AML</th>
<th>CML</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases</td>
<td>21,380</td>
<td>8950</td>
</tr>
<tr>
<td>Deaths</td>
<td>10,590</td>
<td>1080</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>ALL</th>
<th>CLL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases</td>
<td>5970</td>
<td>20,110</td>
</tr>
<tr>
<td>Deaths</td>
<td>1,440</td>
<td>4,660</td>
</tr>
</tbody>
</table>

### Presenting Signs and Symptoms

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

- **CLL**
  - Lymphadenopathy
  - Splenomegaly
  - Hepatomegaly
  - Elevated WBCs
  - Hypogammaglobulinemia
  - “B” symptoms
    - Fever
    - Fatigue
    - Night sweats
    - Unexplained weight loss

### Etiology

- **CML**
  - Risk Factor
    - Radiation exposure
    - Unknown
  - Disease of the older adult

- **CLL**
  - Risk Factors
    - Herbicides used in Vietnam
    - Family history of CLL or any B-cell malignancy
    - Unknown
  - Disease of the older adult

### 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
Philadelphia chromosome. A piece of chromosome 9 and a piece of chromosome 22 break off and trade places. The bcr-abl gene is formed on chromosome 22 where the piece of chromosome 9 attaches. The changed chromosome 22 is called the Philadelphia chromosome.

### 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>
<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 (present in tissues)</td>
<td></td>
</tr>
</tbody>
</table>

### 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

### 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>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Abnormal increase in number of lymphocytes in blood and marrow</td>
</tr>
<tr>
<td>I</td>
<td>Increase in number of lymphocytes and &lt; 3 enlarged lymph node areas</td>
</tr>
<tr>
<td>II</td>
<td>Increase in number of lymphocytes and ≥ 3 enlarged lymph node areas</td>
</tr>
<tr>
<td>III</td>
<td>Same as B and Hemoglobin &lt;10, platelets &lt;100K</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

- 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

Treatment Options

- **CML**
  - Targeted Therapies
    - Tyrosine Kinase Inhibitors (TKI)
      - Imatinib
      - Sorafenib
  - BMT
  - Clinical trial

- **CLL**
  - No current cure
  - “Watch and Wait”
  - Chemotherapy or Targeted Therapies
  - Splenectomy
  - BMT
  - Goals are:
    - Slow growth
    - Provide long periods of remission
    - Improve quality of life

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
Supportive Care

CML
• Leukocytosis:
  – hydroxyurea,
  – leukapheresis,
  – imatinib
• Thrombocytosis:
  – hydroxyurea
  – apheresis

CLL
• Infection prophylaxis
• IVIg for hypogammaglobuline mia

CML: Ongoing Monitoring

• Responding to treatment:
  o Bcr-Abl levels measured every 3 months
  o Bone marrow cytogenetics every year

• Complete cytogenetic response
  o Bcr-Abl levels measured every 3 months
  o 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

Treatment of Advanced Disease

CML: Accelerated Phase
– TKI therapy
– BMT
– Clinical Trial

CML: 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

Risk Factors

AML
– Congenital disorders
– Preceding bone marrow disease
– High doses of radiation
– Benzene
– Tobacco
– Prior chemotherapy
– Family history

ALL
– Radiation
– Exposure to
  o Diesel, gasoline
  o Pesticides
  o Smoking
– Inherited Genetic syndromes
– Largely Unknown
**Presenting Signs and Symptoms**
- Pancytopenia
- WBC elevation
- Pallor
- Petechiae
- Ecchymosis
- Retinal hemorrhages
- Bleeding/bruising
- Gingival hypertrophy
- Cutaneous lesions
- Chloroma

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

**AML: Classification**

WHO (World Health Organization)
- AML with recurrent genetic abnormalities
- AML with multilineage dysplasia
- AML and MDS, therapy-related
- AML not otherwise categorized
- Blast threshold of 20% or any blasts with recurrent genetic abnormalities

FAB (French-American-British)
- 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%

**ALL: WHO Classification**

- Precursor B-cell
  - 4 subtypes based on cytogenetics
- Precursor T-cell
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

- 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

Before Therapy

- HLA typing
- Cardiac function: MUGA scan or echocardiogram
- ALL:
  - Neurological exam/LP
  - Testicular exam
- 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 AML
  - For patients not eligible for BMT, PICC over tunneled catheter is sufficient
  - Implanted port preferred for ALL

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

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

**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

**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

Common Nursing Concerns in Leukemia

• Neutropenia
• Anemia
• Thrombocytopenia
• Mucositis
• Disseminated Intravascular Coagulation

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

• Depression
• Existential distress

Side effects of AML Therapy

• Induction
  – Pancytopenia
  – Tumor Lysis Syndrome (TLS)
  – Mucositis
  – Diarrhea
  – Alopecia
  – Capillary Leak Syndrome

• Consolidation
  – Hand-Foot syndrome
  – Cerebellar toxicity
  – Ocular toxicity

• Longer Term
  ◦ Cardiac toxicity (CHF)

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 Comprehensive Cancer Network
  - www.nccn.org
- National Marrow Donor Program
  - www.marrow.org
- Fertile Hope
  - www.fertilehope.org