LYMPHOMA

Cheryl Kovalski, DO, FACOI
ACOI BOARD REVIEW, 2018
no disclosures
• Solid neoplasm of the immune system characterized by uncontrolled proliferation of cells residing in the lymphoid tissues

• 2016 WHO revised classifications: 93 types
• HODGKIN DISEASE

• ALL OTHER LYMPHOMAS
• Low grade: Small lymphocytic and follicular small cleaved/follicular mixed. Affecting older people, presenting in advanced stage, indolent but incurable.

• Lymph nodes can wax and wane for years

• Survival of untreated disease-years

NONHODGKIN LYMPHOMA (NHL): WHO CLASSIFICATION
• Aggressive (formerly known as Intermediate grade): follicular large cell, diffuse small cleaved/diffuse mixed/diffuse large cell.
• Firm, enlarging mass, +/- B symptoms
• Survival of untreated disease-months
High grade/Highly Aggressive: Immunoblastic, small non-cleaved, lymphoblastic, Burkitts. Wide age range, variable stage, 30-40% long-term remission with intensive treatment.

- Rapidly enlarging lymph node mass
- Survival of untreated disease-weeks
• Lymph node biopsy to evaluate architectural and cytologic features as well as adequate enough to do immunophenotyping.

• FINE NEEDLE ASPIRATE IS INADEQUATE!
NHL: DIAGNOSIS

- Laboratory: CBC, diff, CMP, LDH, SPEP, B2-microglobulin
- Radiography: CT chest/abdomen/pelvis
- PET
- Bone marrow biopsy
- LP with CSF analysis in pts with sinus, epidural, testis dz or those prone to have circulating tumor cells-Burkitts, lymphoblastic
STAGING

I  Involvement of 1 lymph node or 1 extralymphatic site (IE)

II Involvement of 2 or more lymph node regions or localized extralymphatic disease and involved lymph nodes on the same side of the diaphragm (IIE)
III Involvement of lymph node regions on both sides of the diaphragm, +/- localized extralymphatic disease (IIIE), spleen (IIIS), or both (IIIES)

IV Diffuse or disseminated involvement of 1 or more extralymphatic organs or tissues with or w/o LN involvement
A  Asymptomatic

B  Fever, night sweats and/or unexplained weight loss of 10% or more of body weight in past 6 months

Only used for Hodgkin lymphoma
Treatment

- Rituxan is added to treatment of B cell lymphoma that is CD 20 positive
- Low grade: Rituxan, bendamustine, CVP, CHOP
- Aggressive grade: R-CHOP (cytoxan, adriamycin, oncovin, prednisone)
- Highly aggressive: Hyper CVAD, high dose methotrexate
HODGKIN DISEASE

- 1% of all malignancies in US
- First malignancy to demonstrate curative potential of combination chemotherapy
- Most common in young adults; bimodal peak in 3rd and 7th decades
- Association with Epstein-Barr virus
- Arises from B lymphocytes
• Differentiated from other lymphomas by the presence of large binucleate or multinucleate cell, Reed Sternberg cell

(Giant “owl eyes”)
HODGKIN DISEASE

- Nodes are painless and rubbery, most commonly found in neck and mediastinum.
- Most common etiology of mediastinal mass in young person.
- Unusual symptoms of pruritus, alcohol-induced pain in involved lymph node sites, sweats, fevers; intermittent “Pel-Ebstein” fever rare.
HD: HISTOPATHOLOGIC SUBTYPES

- Lymphocyte Predominant
- Nodular Sclerosis
- Mixed Cellularity
- Lymphocyte Depleted
- Nodular lymphocyte predominant
HD: POOR PROGNOSTIC FACTORS

- Advanced Stage
- Large mediastinal mass (ratio>0.33)
- Systemic symptoms
- Extra nodal disease
- Advanced age
- Male sex
HD: TREATMENT

• Favorable Stage I and IIA: 2-4 cycles chemotherapy and involved field RT
• Limited HD with risk factors: Full chemotherapy & involved field RT
• Advanced HD: Full chemotherapy and RT only for pts with bulky mediastinal disease
• Bone marrow transplant usually considered after first relapse
• ABVD is standard regimen (adriamycinc, bleomycin, vinblastine, dacarbazine)
HD: LATE EFFECTS OF TREATMENT

- Mantle RT: hypothyroid, heart disease lung & breast cancer
- Para-aortic or splenic: gastric cancer
- MOPP chemotherapy: acute leukemia sterility
HODGKINS SURVIVAL

- STAGE
  - IA-IIA 80-90 %
  - IB-IIB 80-85 %
  - IIA 75-80 %
  - IIIA 75-80 %
  - IIIB 60%
  - IVA-B 60%
LEUKEMIA

no disclosures
# Abnormalities of Cellular Proliferation in AL

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>Leukemic</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stem Cells</strong></td>
<td>Normal</td>
<td>Abnormal</td>
</tr>
<tr>
<td><strong>Maturation</strong></td>
<td>Synchronous with proliferation; terminates division</td>
<td>Asynchronous Does not terminate division</td>
</tr>
<tr>
<td><strong>Feedback</strong></td>
<td>Controls production</td>
<td>Absent or ineffective</td>
</tr>
<tr>
<td><strong>Steady State</strong></td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>Release</strong></td>
<td>Orderly</td>
<td>Random</td>
</tr>
<tr>
<td><strong>End Product</strong></td>
<td>Mature cells-cannot resume division</td>
<td>Immature cells-can resume division</td>
</tr>
</tbody>
</table>
LEUKEMIA CLASSIFICATION

ACUTE: LYMPHOCYTIC      NONLYMPHOCYTIC

CHRONIC: LYMPHOCYTIC    MYELOGENOUS
ACUTE LEUKEMIA

A DIVERSE GROUP OF NEOPLASMS ARISING FROM TRANSFORMATION OF UNCOMMITTED OR PARTIALLY COMMITTED HEMATOPOIETIC STEM CELLS
ACUTE LEUKEMIA PATHOGENESIS

- Leukemic cell abnormalities: cytogenetic abnormality leading to clonal proliferation of leukemic cell; maturation arrest of leukemic cells

- Leukemic cells inhibit normal cell lines from proliferating leading to: anemia, bleeding, infection; electrolyte imbalance; leukostasis

- Invasive & infiltrative effects
ACUTE LEUKEMIA: PRESENTATION

- Symptoms of only a few weeks duration
- Symptoms reflect bone marrow failure +/- involvement of extramedullary sites
- Fever, documented infections in up to half
- Symptomatic anemia
- May have bleeding, but hemorrhage rare
- Bone pain, fatigue
ACUTE LYMPHOCYTIC LEUKEMIA

- Mainly occurs in children - peak ages: 2-8, >60
- Worse prognosis with: increasing age
- Philadelphia chromosome
- WBC >30K
- Sex: equal
- Rare in blacks
ALL-PREDISPPOSING FACTORS

- Irradiation early in life
- Ataxia telangiectasia
- Mongolism
- Leukemia in family
- Identical twin
## ALL FAB CLASSIFICATION

<table>
<thead>
<tr>
<th>FAB Class</th>
<th>Cell Size</th>
<th>Nucleus</th>
<th>Cytoplasm</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>L1</strong></td>
<td>Small homogeneous</td>
<td>Round, occasional cleft or fold; homogeneous, finely dispersed chromatin; nucleoli small or not visible</td>
<td>Usually scanty slight to moderate basophilia</td>
</tr>
<tr>
<td><strong>L2</strong></td>
<td>Large heterogeneous</td>
<td>Fine to coarse chromatin; clefts 1 or more nucleoli</td>
<td>Abundant, variable basophilia</td>
</tr>
<tr>
<td><strong>L3</strong></td>
<td>Large homogeneous</td>
<td>Oval to round, dense finely stippled chromatin; 1 or more prominent nucleoli</td>
<td>Moderately abundant, intensely basophilic, prominent vacuoles</td>
</tr>
</tbody>
</table>
ACUTE LYMPHOCYTIC LEUKEMIA: PRESENTATION

- Half have hepatomegaly, splenomegaly &/or lymphadenopathy
- Mediastinal masses primarily in T cell lineage ALL
- <10% with CNS involvement
- Other sites of extramedullary involvement: testis, retina, skin, any organ infiltrated
ALL: ADDITIONAL CLINICAL FEATURES

- C ALL: most common in children; lymphadenopathy common; gum, skin, mediastinal infiltration uncommon; muramidase staining-low or normal

- T cell ALL: most common in 2nd & 3rd decades; blasts more common in blood; frequent extra medullary disease-CNS, mediastinum

- B cell ALL: no distinct findings; responds poorly to conventional therapy

- Ph-positive ALL: shorter remissions than C ALL
ALL: GOOD PROGNOSTIC FEATURES

- Age less than 35 (best 3-9)
- WBC < 30,000
- Blasts < 80%
- Early complete remission after start of chemotherapy
- Absence of translocations
- Presence of hyperdiploid state
- CALLA+ phenotype
- Female
DIAGNOSIS

- Lymphoblasts seen on blood smear and bone marrow
  
  May be difficult to distinguish from myeloblasts

  Flow cytometry helpful in differentiating ALL from AML

- Evaluate CSF for CNS involvement
ALL: TREATMENT

- Daunorubicin, Vincristine and Corticosteroids are key drugs in induction
- Maintenance therapy at least 2 years
- CNS Prophylaxis
- Imatinib in Ph+ with chemotherapy
- Radiation in bulky mediastinal disease
- SCT if poor prognostic features or progressive disease
ACUTE NONLYMPHOCYTIC LEUKEMIA

- Group of marrow based malignancies, clinically similar, BUT DISTINCT morphologically, immunophenotypically, and cytogenetically
- Must distinguish from ALL
- More common in adults
## AML FAB CLASSIFICATION

<table>
<thead>
<tr>
<th>FAB Class</th>
<th>Predominant cell type</th>
</tr>
</thead>
<tbody>
<tr>
<td>M1: undifferentiated myelocytic</td>
<td>Myeloblasts</td>
</tr>
<tr>
<td>M2: myelocytic</td>
<td>Myeloblasts, promyelocytes, myelocytes, blasts</td>
</tr>
<tr>
<td>M3: promyelocytic</td>
<td>Promyelocytes, blasts</td>
</tr>
<tr>
<td>M4: myelomonocytic</td>
<td>Promyelocytes, myelocytes, proonocytes, monocytes, blasts</td>
</tr>
<tr>
<td>M5: monocytic</td>
<td>Monoblasts, myeloblasts</td>
</tr>
<tr>
<td>M6: erythroleukemia</td>
<td>Erythroblasts, myeloblasts</td>
</tr>
<tr>
<td>M7: megakaryocytic leukemia</td>
<td>Abnormal appearing megakaryocytes myeloblasts</td>
</tr>
</tbody>
</table>
ANLL RISK FACTORS

- Exposure to ionizing radiation
- Exposure to chemicals: benzene, chloramphenicol, phenylbutazone
- Exposure to drugs: alkylating agents and topoisomerase II inhibitors
- Genetic factors: Mongolism, Bloom’s syndrome, Fanconi’s anemia
- MDS, Myelofibrosis, Polycythemia, CGL
ANLL PROGNOSTIC FACTORS

Worse if

- Age > 60
- Poor performance status
- AML secondary to prior chemotherapy or bone marrow dysfunction
- WBC > 20K
CLINICAL FEATURES

- S & S secondary to anemia, thrombocytopenia, leukopenia or leukocytosis

- Hyperleukocytosis (>100K blasts): most common in hyper granular APL causing obstruction, vascular injury and hypoxia (due to pulmonary congestion) & ischemia increasing risk of stroke

- Coagulation abnormalities: abnormal platelet function; consumption (DIC)-M3>M4 or M5

- Typhilitis-mimics appendicitis

- Metabolic abnormalities: tumor lysis syndrome; renal tubular dysfunction

- Extramedullary : granulocytic sarcoma-M5, soft tissue involvement-skin, gingiva, lungs, lymph nodes(splenomegaly uncommon), CNS: headache, mental status change, nerve palsy
GRANULOCYTIC SARCOMA
ANLL: LABORATORY FEATURES

- Anemia universally present; reticulocyte count low
- Thrombocytopenia nearly always present (decreased production & survival)
- Leukopenia in 20% with absolute neutropenia
- Leukocytosis >50%; myeloblasts almost always present in blood
- Auer rods <10%
AUER RODS
ANLL: BONE MARROW FINDINGS

- Blasts
- Decrease in normal blood cell progenitors
- Cytogenetics performed to identify any genetic abnormality diagnostic of a particular FAB class
- Immunophenotyping
ANLL: IMMUNOPHENOTYPE

- May help establish diagnosis, more precise than morphology alone
- Distinguishes ALL from ANLL, identifies subtypes, recognizes biphenotypic
- Characteristic ANNL: CD 13 & 33+
- Often CD 11 & 14+
- CD34 unfavorable
- Lymphoid markers may be expressed
ANLL: TREATMENT

- Address concurrent medical problems

- Supportive care:
  - Blood product transfusion
  - Broad spectrum antibiotics for fever and neutropenia
  - Antifungal & antiviral therapy
  - Nutrition
ANLL: THERAPY

- Remission induction: 7+3 regimen: ARA-C + daunorubicin= 60-80% CR

- Postremission therapy:
  - Consolidation with Ara-C
  - Allogeneic SCT

- APL: ATRA + chemotherapy
CHRONIC LEUKEMIA

no disclosures
Most common leukemia in Western world
Median age at diagnosis: 65
Median survival: 9 years
Advanced disease has increased morbidity and mortality from infection: T cell dysfunction, lack of ability to make Ig, results of treatment
CLL: DIAGNOSIS

- Lymphocytosis (ALC > 5000) small, mature lymphocytes
- Bone marrow involvement >30% lymphs
- < 55% atypical/immature lymphoid cells in peripheral blood
- Clonal expansion of abnormal B lymphs
  - B-cell surface ags (CD 5, 19, 20, 23)
CLL: CLINICAL COURSE

• Incidental finding of lymphocytosis

• Asymptomatic at time of diagnosis and for a prolonged period of time
CLL CLINICAL COURSE

- Progressive bone marrow impairment
- Progressive neutropenia and hypogammaglobulinemia increasing risk of infection
- Autoimmune phenomena
- Richter’s transformation
CLL: AUTOIMMUNE COMPLICATIONS

- Coombs’ + hemolytic anemia in 15%
- ITP
- Pure red cell aplasia
- Granulocytopenia
## CLL: Rai Staging

<table>
<thead>
<tr>
<th>Stage</th>
<th>Risk</th>
<th>Features</th>
<th>Surv yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Low</td>
<td>Lymphocytosis</td>
<td>&gt; 12</td>
</tr>
<tr>
<td>I</td>
<td>Intermediate</td>
<td>Adenopathy</td>
<td>8</td>
</tr>
<tr>
<td>II</td>
<td>Intermediate</td>
<td>Splenomegaly +/- Hepatomegaly</td>
<td>6</td>
</tr>
<tr>
<td>III</td>
<td>High</td>
<td>Anemia</td>
<td>1.6</td>
</tr>
<tr>
<td>IV</td>
<td>High</td>
<td>Thrombocytopenia</td>
<td>1.6</td>
</tr>
</tbody>
</table>
CLL: POOR PROGNOSIS

- Advanced stage at diagnosis
- Short lymphocyte doubling time (6 mos)
- Diffuse pattern of marrow infiltration
- Advanced age/male
- 17p or 11q deletion
- High serum levels of B2 microglobulin and CD23
- CLL-PLL
- Richter’s syndrome
CLL TREATMENT

• Incurable
• Observation is appropriate for early stage or asymptomatic CLL
• No proven advantage to early chemotherapy if asymptomatic
CLL: INDICATIONS FOR TREATMENT

• B Symptoms secondary to CLL: weight loss >10%, night sweats, fever
• Progressive marrow failure
• Massive splenomegaly
• Massive lymphadenopathy
CLL: INDICATIONS FOR TREATMENT

• Progressive lymphocytosis, >50% increase over 2 mos or lymphocyte doubling time <6 mos
• Richter’s syndrome-transformation from low to high grade lymphocytic malignancy
• Hemolytic anemia
• ITP
CLL: TREATMENT

- Alkylating agents: bendamustine, chlorambucil, cyclophosphamide
- Corticosteroids
- Purine analogs: fludarabine, cladribine, pentostatin
- Monoclonal abs: Rituximab, Alemtuzumab
HAIRY CELL LEUKEMIA

• Rare B-cell leukemia
• Median age of onset: 55
• Strong male predominance
• Presents with pancytopenia and massive splenomegaly
• Characteristic “dry tap” bone marrow due to hypercellularity
HAIRY CELL LEUKEMIA
HAIRY CELL LEUKEMIA

- TRAP +
- Treatment with 2-CDA (cladribine) or Pentostatin induces complete remission in most
CHRONIC MYELOGENOUS LEUKEMIA

• Clonal myeloproliferative disorder of pluripotent stem cells affecting all cell lines
• Cytogenetic hallmark: Philadelphia chromosome (9;22)
• Molecular hallmark: BCR/ABL
• 7–15% adult leukemias
• Median age: 45–55; 20–30% >60
CML: PRESENTATION

• 85% in chronic phase at diagnosis
• 5% Ph negative
• Symptoms:
  • Most asymptomatic, only leukocytosis
  • LUQ discomfort and early satiety secondary to splenomegaly
  • Unusual infections
PHILADELPHIA CHROMOSOME
PHILADELPHIA CHROMOSOME

Translocation 9;22 = BCR-ABL rearrangement
Leukemia phenotype  Incidence
CML            95%
ALL            25-30% adult
      5% children
AML            1-2%
## CML Phases

<table>
<thead>
<tr>
<th></th>
<th>Chronic</th>
<th>Accelerated</th>
<th>Blastic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Past</td>
<td>3-5 years</td>
<td>12-18 months</td>
<td>3-9 months</td>
</tr>
<tr>
<td>Present</td>
<td>25+ years</td>
<td>4-5 years</td>
<td>6-12 months</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>Blasts ( \geq 15% )</td>
<td>Blasts &gt;29%</td>
<td>Extramedullary disease with localized immature blasts</td>
</tr>
<tr>
<td></td>
<td>Bl+Pros &gt;29%</td>
<td>Basophils &gt;19%</td>
<td>Platelets &lt;100K Clonal evolution</td>
</tr>
</tbody>
</table>
CML WORK-UP

Physical exam: performance status, splenomegaly
CBC, diff, chem pro
Bone Marrow
Cytogenetics
CML: CURRENT TREATMENT RECOMMENDATIONS

Frontline:
- Imatinib, Nilotinib, Dasatinib

Imatinib failure:
- nilotinib, dasatinib, bosutinib

Allogeneic SCT