MALIGNANT HEMATOLOGY

ACOI BOARD REVIEW, 2015

Cheryl Kovalski, DO FACOI
Leukemia
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: 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
- Worse prognosis with:
  - increasing age,
  - Philadelphia chromosome,
  - WBC > 30K
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
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
ANLL RISK FACTORS

- Exposure to ionizing radiation
- Exposure to chemicals: Benzene
- Exposure to drugs: alkylating agents and topoisomerase II inhibitors
- Genetic factors
- MDS
ANLL PROGNOSTIC FACTORS

Worse if

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

- S & S secondary to anemia, thrombocytopenia, leukopenia or leukocytosis
Hyperleukocytosis (>100K blasts): most common in microgranular Acute Progranulocytic Leukemia causing obstruction, vascular injury, & hypoxemia resulting in stroke or pulmonary congestion
ANLL: CLINICAL FEATURES

- Coagulation abnormalities
  - abnormal platelet function
  - consumption: M3 > M4, M5
- Typhlitis (mimics appendicitis)
ANLL: CLINICAL FEATURES

- Metabolic abnormalities
  - tumor lysis syndrome
  - renal tubular dysfunction
ANLL: CLINICAL FEATURES

- Extramedullary presentation: granulocytic sarcoma-M5, rare, increased soft tissue involvement (skin, gingiva, lymph nodes, lungs, CNS)

- Splenomegaly uncommon
ANLL: LABORATORY FEATURES

- Anemia universally present
- Thrombocytopenia nearly always present (decreased production & survival)
- Leukopenia in 50% with absolute neutropenia
- Myeloblasts almost always present in blood
- Auer rods
AUER RODS
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 LYMPHOCYTIC LEUKEMIA (CLL)

- 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 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Low</td>
<td>Lymphocytosis</td>
<td>&gt;12</td>
</tr>
<tr>
<td>I</td>
<td>Inter-</td>
<td>Lymphadenopathy</td>
<td>7</td>
</tr>
<tr>
<td>II</td>
<td>mediate</td>
<td>Splenomegaly +/- Hepatomegaly</td>
<td>5</td>
</tr>
<tr>
<td>III</td>
<td>High</td>
<td>Anemia</td>
<td>2-5</td>
</tr>
<tr>
<td>IV</td>
<td></td>
<td>Thrombocytopenia</td>
<td></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 >20%, 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

Diagram showing the process of the Philadelphia chromosome formation:

- Normal chromosome 9
- Normal chromosome 22
- Chromosomes break
- Changed chromosome 9
- Changed chromosome 22 (Philadelphia chromosome)

Key markers:
- bcr
- abl
- bcr-abl

© 2007 Terese Winslow
U.S. Govt. has certain rights
Translocation 9;22 = BCR-ABL rearrangement

<table>
<thead>
<tr>
<th>Leukemia phenotype</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>CML</td>
<td>95%</td>
</tr>
<tr>
<td>ALL</td>
<td>25-30% adult</td>
</tr>
<tr>
<td></td>
<td>5% children</td>
</tr>
<tr>
<td>AML</td>
<td>1-2%</td>
</tr>
</tbody>
</table>
## CML: PHASES

<table>
<thead>
<tr>
<th>Phase</th>
<th>Duration</th>
<th>Blasts ≥15%</th>
<th>Blasts ≥30%</th>
<th>Bl + Pro ≥30%</th>
<th>Basophils ≥20%</th>
<th>Plts &lt; 100,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic</td>
<td>3-5 yrs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Accelerated</td>
<td>12-18 mos</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blast Crisis</td>
<td>3-9 mos</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Blasts: Blast cells
- Bl + Pro: Blasts + Promyelocytes
- Plts: Platelets
CML: TREATMENT

OBJECTIVES

- **MODALITY**
  - Hydrea, Busulfan
  - Interferon alpha
  - TKIs-Imatinib
  - nilotinib, dasatinib
  - Allogeneic SCT
<table>
<thead>
<tr>
<th>Year</th>
<th>Total</th>
<th>Dead</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1975</td>
<td>106</td>
<td>106</td>
</tr>
<tr>
<td>1975-1982</td>
<td>110</td>
<td>106</td>
</tr>
<tr>
<td>1983-1990</td>
<td>165</td>
<td>128</td>
</tr>
<tr>
<td>1991-2000</td>
<td>352</td>
<td>147</td>
</tr>
<tr>
<td>2001-present</td>
<td>415</td>
<td>35</td>
</tr>
</tbody>
</table>
Poor Prognostic Factors

BEFORE TKIs

- Older age
- Splenomegaly
- Anemia
- Thrombocytosis or Thrombocytopenia
- Blasts, promyelocytes, basophils
- Marrow fibrosis
- Cytogenetic clonal evolution
CML WORK-UP

- Physical exam: performance status, splenomegaly
- CBC, diff, chem pro
- BM, cytogenetics with FISH & QPCR
CML: CURRENT TREATMENT RECOMMENDATIONS

- Frontline: Imatinib 400 mg/d; nilotinib 300-400 mg Bid; dasatinib 100 mg/d
- Imatinib failure: nilotinib, dasatinib, bosutinib
- Allogeneic SCT
- Investigational
- Combining TKIs + old standards (hydrea)
CML MONITORING

- **FISH and QPCR q 6 mos**
- **Bone marrow cytogenetics q 2-3 yrs; more often if abnormalities noted**
- **Mutation analysis only if imatinib failure or change of treatment**
MYELOPROLIFERATIVE NEOPLASMS (MPN)

Classic

- Polycythemia vera
- Essential thrombocythemia
- Primary myelofibrosis
Risk stratification for thrombosis in ET and PV

- **Low risk**
  - Age < 60
  - No hx of thrombosis
  - Plt ct <1 million

- **High risk**
  - Age 60 or greater
  - or previous thrombosis
ET and PV treatment recommendations

- Low risk: ASA
- High risk: Hydroxyurea + asa
- Phlebotomy to maintain Hct < 45
LYMPHOMA
• Solid neoplasm of the immune system characterized by uncontrolled proliferation of cells residing in the lymphoid tissues.
• 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
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
NHL: WHO CLASSIFICATION

- 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
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
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
HD: LATE EFFECTS OF TREATMENT

• Mantle RT: hypothyroidism
tung & breast cancer
heart disease

• Para-aortic or splenic: gastric cancer

• MOPP chemotherapy: acute leukemia
sterility
HODGKINS SURVIVAL

- **STAGE**
  - IA-IIA 80-90%
  - IB-IIB 80-85%
  - IIIA 75-80%
  - IIIB 60%
  - IVA-B 60%
MULTIPLE MYELOMA
PLASMA CELL DISORDERS

- Multiple Myeloma
- Monoclonal Gammopathy of Undetermined Significance (MGUS)
- Smoldering Multiple Myeloma (SMM)
- Solitary Plasmacytoma
- Waldenstrom’s Macroglobulinemia
- Amyloidosis
- POEMS
MULTIPLE MYELOMA: CLINICAL PRESENTATION

- Weakness and fatigue
- Bone pain
- Fractures
- Infection
- Renal failure
- Hypercalcemia
MULTIPLE MYELOMA: CLINICAL PRESENTATION

- Plasma cells in bone marrow - 96%
- Monoclonal (M) Protein - 93%
- Anemia - 73%
- Lytic Bone Lesions - 67%
- Renal insufficiency SCr ≥ 2-19%
- Hypercalcemia ≥ 11-13%
MULTIPLE MYELOMA

Plasma cell

Rouleux formation
M PROTEIN IN MYELOMA

- IgG (50%)
- IgA (20%)
- Light chain only (20%)
- Rarely IgD (2%)
MYELOMA WORK-UP

- Serum Protein Electrophoresis (SPEP) only identifies an M spike
- Immunofixation (IFX) identifies type and clonality (kappa/lambda)
- 24 hour urine for PEP and IFX
- Skeletal survey
- Bone marrow biopsy
- CBC, serum creatinine, calcium, CMP
- B-2 microglobulin
MYELOMA DIAGNOSIS

- Evidence of monoclonal plasma cell disorder in serum or bone marrow
- Plus at least one or more of the following:
  - Renal insufficiency
  - Lytic bone lesions
  - Anemia
  - Hypercalcemia
MYELOMA: TREATMENT

- Melphalan / Prednisone: avoid melphalan if transplant candidate
- Revlamid +/- Decadron
- Velcade +/- Decadron
- Traditional chemotherapy
- Stem cell transplant
- Bisphosphonates
MGUS

- M spike < 3 grams and
- Plasma cells in bone marrow <10%
- No anemia or bone lesions
- Normal calcium and kidney function
SMM

- M spike >3 grams OR
- Bone marrow plasma cells >10%
- No anemia or bone lesions
- Normal calcium and kidney function
SOLITARY PLASMACYTOMA

- Single bony or extramedullary lesion
- M protein may be present
- Bone marrow: Negative
- Treatment: Radiation
- Median survival: 10 years
- 55% later develop myeloma
WALDESTROMS MACROGLOBULINEMIA

AKA Lymphoplasmacytic lymphoma,
A type of NHL which produces large amounts of abnormal proteins/macroglobulin
WALDENSTROM’S MACROGLOBULINEMIA

- IgM in serum
- Lymphoplasmacytoid appearance of cells in the marrow
- Adenopathy
- Hyperviscosity syndrome
WALDENSTROMS MACROGLOBULINEMIA

- Treatment
  - Fludarabine & Cyclophosphamide
  - Decadron
  - Rituximab
  - Velcade

- Plasmapheresis if symptomatic hyperviscosity syndrome
AMYLOIDOSIS

Group of diseases characterized by deposition of insoluble protein in organs and tissues resulting in organ dysfunction; classification based on the precursor proteins that form fibril deposits.

Diagnosis requires presence of amyloid fibers, typically in fat pad aspirate, stained with Congo Red reveals apple green birefringence under polarized light.
AMYLOIDOSIS

Consider diagnosis if:

- Non-diabetic nephrotic syndrome
- Non-ischemic cardiomyopathy with an echo showing LVH
- Hepatomegaly or alk phos elevation without imaging abnormality
- Peripheral neuropathy with MGUS or CDP with autonomic features
- Atypical myeloma monoclonal light chains in urine and modest marrow plasmacytosis
AMYLOIDOSIS

- Primary (AL) (light chain)
- Familial (mutated TTR)
- Secondary (SAA; protein A)
- Senile (unmutated TTR)
- Dialysis associated (beta 2-microglob)
AMYLOIDOSIS

Primary: Fibrils are Ig light chains (AL)
Deposited in heart, tongue, GI tract and skin. 21% have MM

Secondary: Fibrils are protein A (AA)
Deposited in liver, kidney and skin.

Treatment: Alkylating agents, prednisone, Stem cell transplant, Velcade
POEMS SYNDROME

Overproduction of light chains, usually lambda, without significant plasma cells in marrow, many organ systems involved
POEMS SYNDROME

- Polyneuropathy-usually sensory
- Organomegaly-liver and spleen most common
- Endocrinopathies
- M protein
- Skin changes-hypertrichosis, thickening
- Sclerotic bone lesions
MYELODYSPLASTIC SYNDROME
MDS

- Heterogeneous group of clonal stem cell disorders with a variable clinical course
- Characterized by proliferation and ineffective maturation of hematopoietic precursors
- Results in pancytopenia
- Incidence increases with age
MDS ETIOLOGY

- TOXIC EXPOSURE: Smoking, Benzene
- SECONDARY-THERAPY RELATED: Chemo, RT
- INHERITED DISORDERS - Fanconi anemia
- DE NOVO
MDS ABNORMALITIES

QUANTITATIVE
- Anemia
- Neutropenia
- Thrombocytopenia
- Monoclonal Proteins
- Autoimmune Features

QUALITATIVE
- Abnormal RBC
- Impaired neutrophil function
- Impaired platelet function
- Impaired immune regulatory function
MDS WHO CLASSIFICATION, 2008

- Refractory cytopenia with unilineage dysplasia
- Refractory cytopenias with multilineage dysplasia
- Refractory Anemia with Ringed Sideroblasts
- Refractory Anemia with Excess Blasts (RAEB-1 5-9%; RAEB-2 10-19% blasts)
- 5q- syndrome
- Unclassifiable
- Childhood MDS
MDS CYTOGENETICS

- Very Favorable: del(11q), -Y
- Favorable: 5q-, 20q-, normal
- Intermediate: Trisomy 8
- Unfavorable: Monosomy 7, 7q-, Multiple
MDS PROGNOSTIC FEATURES

- Percent Blasts
- Cytogenetics
- Number of Cell Lines Involved
- Age
- Primary vs. Secondary
MDS TREATMENT

- EPO
- Dacogen
- Vidaza
- Revlamid for 5q- syndrome only
- Bone Marrow/Stem Cell Transplant
THANK YOU!