Leukemia and MDS
Edwin P. Alyea, M.D.

- Chronic Lymphocytic Leukemia
- Acute Lymphocytic Leukemia
- Myelodysplastic Syndromes
- Acute Myeloid Leukemia
- Chronic Myelogeneous Leukemia

Disclosures
Edwin P. Alyea

- None

Objectives

- Incidence
- Diagnosis
  - Histology
  - Immunophenotyping
  - Cytogenetics
- Prognosis/Risk Stratification
- Treatment Options

Chronic Lymphocytic Leukemia

- Most common form of leukemia
- Heterogeneous disease
- Median age at diagnosis is 65
- Involves the bone marrow, lymph nodes and spleen at diagnosis
- Malignant cell is a B lymphocyte
- Common complications include autoimmune hemolytic anemia and hypogammaglobulinemia
- Increased risk of secondary malignancies

Rai Staging System

<table>
<thead>
<tr>
<th>Stage</th>
<th>Features</th>
<th>Median Survival (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Lymphocytosis</td>
<td>14.5</td>
</tr>
<tr>
<td>I</td>
<td>+ adenopathy</td>
<td>7.5</td>
</tr>
<tr>
<td>II</td>
<td>+ spleen/liver enlargement</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>Anemia</td>
<td>2.5</td>
</tr>
<tr>
<td>IV</td>
<td>Thrombocytopenia</td>
<td></td>
</tr>
</tbody>
</table>

Prognostic Factors in CLL

<table>
<thead>
<tr>
<th>Factor</th>
<th>Median Survival (yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone Marrow</td>
<td></td>
</tr>
<tr>
<td>Nodular</td>
<td>14</td>
</tr>
<tr>
<td>Diffuse</td>
<td>4</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td></td>
</tr>
<tr>
<td>≤ 50,000</td>
<td>12</td>
</tr>
<tr>
<td>&gt; 50,000</td>
<td>4</td>
</tr>
<tr>
<td>Lymphocyte</td>
<td></td>
</tr>
<tr>
<td>&gt; 12 months</td>
<td>15</td>
</tr>
<tr>
<td>≤ 12 months</td>
<td>6</td>
</tr>
<tr>
<td>Doubling Time</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>&gt; 10</td>
</tr>
<tr>
<td>Abnormal</td>
<td>5-6</td>
</tr>
</tbody>
</table>
Genetic Aberrations and Survival

Dohner et al., NEJM 2000

Therapy for Early Stage CLL Does Not Change Survival

Dighiero et al., NEJM 1998

### Fludarabine
- Purine analogue
- higher response rate with combination chemotherapy
  - Fludarabine + Rituxan (FR)
  - Fludarabine, Cyclophosphamide and Rituxan (FCR)

Side Effects
- myelosuppression
- tumor lysis syndrome
- hemolytic anemia
- opportunistic infections
  - should not combine with Prednisone
  - PCP prophylaxis should be given

### Alemtuzumab
- Relapsed or refractory CLL
- Patients with 17p deletion
- Antibody against CD52
- Side effects:
  - Low blood counts
  - Infusion reactions
  - CMV reactivation

### New Agents in CLL
- Chemotherapy
  - Bendamustine—often combined with Rituxan (BR)
- BCL-2 antagonists
  - Navitoclax—30% activity in relapsed pts
  - ABT-199—second generation molecule lacking interaction with bcl-xl; in early phase I testing
- CDK Inhibitors
  - Flavopiridol
  - Dinaciclib
- B-cell receptor kinase inhibitors
  - CAL-101: Selective orally available PI3K-δ inhibitor
  - PCI-32765: A Potent Btk Inhibitor

### Infectious Complications in CLL
- Hypogammaglobulinemia common
  - infections with encapsulated organisms
  - replacement therapy indicated for patients with recurrent infections
- Progressive granulocytopenia
- Severe T cell immune suppression
  - infections with listeria, PCP, etc.
  - Fludarabine leads to reduction in CD4+ T cell counts
  - need PCP prophylaxis
  - CMV reactivation with alemtuzumab
Other Complications of CLL

- Autoimmune Complications
  - Hemolytic anemia
    - seen after treatment with fludarabine
  - ITP
    - steroids, IgIV
- secondary malignancies- increased risk
- risk of transformation to more aggressive disease
  - rapidly enlarging nodes, rapid increase in LDH, B symptoms

Acute Lymphocytic Leukemia

- Most common form of childhood cancer
- peak incidence 3-5 years, bimodal peak at 50
- increased incidence in patients with Down’s syndrome, Bloom’s Syndrome and Ataxia-Telangiectasia
- represents about 15% of leukemia in adults

Adverse Prognostic Features in ALL

<table>
<thead>
<tr>
<th>Adverse Feature</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>&gt;35</td>
</tr>
<tr>
<td>High WBC at Presentation</td>
<td>&gt;25,000</td>
</tr>
<tr>
<td>Cytogenetics</td>
<td>Ph+ (9;22), 11q23, +8</td>
</tr>
<tr>
<td>Delayed Response to induction therapy</td>
<td>&gt;4-6 weeks to obtain remission</td>
</tr>
</tbody>
</table>

Treatment of ALL

- Induction Therapy- 5 drug regimen
  - (cytoxan, adriamycin, L-aspariginase, vincristine and prednisone)
- Consolidation therapy-
  - CNS prophylaxis
  - Maintenance chemotherapy extends for about 2 years
- 5 year leukemia free survival: 30%- 40%

Risk Adapted Therapy

First Complete Remission

- High Risk Patients
  - Poor Risk Cytogenetic Abnormalities (i.e. 9;22)
  - Adverse features (advanced age, high WBC, etc)
  - Allogeneic Bone Marrow Transplantation in first remission
- Standard Risk (T cell or No adverse features)
  - chemotherapy
  - Bone Marrow Transplantation

Ph+ ALL

- Incidence: 25% of adults, >40% -50% of patients over 60
- Diagnosis: FISH or cytogenetics
- Minimal residual disease monitoring by PCR
  - 9;22 translocation
    - Bcr-abl; chromosome 9-ABL and chromosome 22 BCR
    - p190 in 70%
    - p210 in 30%
- Treatment
  - Chemotherapy plus imatinib
  - Stem Cell Transplantation
  - ?imatinib or dasatinib being explored
Special Issues in ALL

- Infections
  - use of prednisone increases risk for infections such as PCP. PCP prophylaxis should be given.
- Avascular Necrosis
  - related to prior steroid therapy
- Sites of Relapse
  - Both the CNS and testicles are potential sites of relapse.

Myelodysplastic Syndrome

- Heterogenous group of clonal disorders characterized by inadequate and dysmorphic hematopoiesis
- Stem cell disorder
- Increased incidence with age
- Increased risk with prior chemotherapy or radiation
- Cytopenias present at diagnosis
  - Anemia 45-90%
  - Thrombocytopenia 20-40%
  - Neutropenia 25-40%

Bone Marrow Findings in MDS

- hypercellular marrow
- trilineage dysplasia
- irregular nuclear formations in red cell precursors

From Heaney, NEJM 1999

Differential Diagnosis of MDS

- Anemia of chronic disease
- marrow infiltration
- drug toxicity (ETOH, chemotherapy, INH)
- viral infections (HIV)
- vitamin deficiency (B12, folate)

The MCV is often elevated in patients with MDS

Prognosis in MDS

MDS Scoring System

Risks of MDS
- infection
- bleeding
- progression to acute leukemia

Factors considered in the MDS Scoring system
- % Blasts in the BM
- Cytogenetics
- Number of cytopenias

International MDS Classification Index


percent marrow blasts, karyotype score, number of cell lines depressed

Survival

Years

Freedom from AML Evolution

Years

Low

Int-1

Int-2

High
Treatment of MDS

- Treatment: Age, Performance status and IPSS
- Supportive Care
  - Chelation therapy for iron overload
- RARS-may respond to pyridoxine
- Growth Factors:
  - EPO-helpful if EPO level is less than 500
  - G-CSF for patients with recurrent infections
- Chemotherapy
  - 5-azacytidine-hypomethylation agent
  - Decitibine-inhibits DNA methylation
  - Lenalidomide (5q-)
- Allogeneic Bone Marrow Transplant
  - only curative option

Special Issues in MDS

- 5q- syndrome
  - older women with anemia and high platelet counts
  - prolonged course
  - Lenalidomide associated with response
- Hypoplastic MDS
  - hypocellular bone marrow
  - DDX with aplastic anemia. Cytogenetics are helpful.
- Therapy related MDS
  - prior radiation and chemotherapy exposure
  - 11q23 abnormalities associated with epipodophylotoxins (VP-16)

Acute Myelogenous Leukemia

- Incidence of 2.4/100,000
- median age of 65-70
- most common acute leukemia in adults
- associated with prior radiation and toxin exposure
- may arise from prior MDS

Bone Marrow Findings in AML

- Histology
  - large blasts
  - nucleoli often visible
  - granules often present
  - Auer rods may be present
- Immunophenotyping demonstrates myeloid makers
  - CD13, CD33, CD11

From Lowenberg, NEJM 1999

Cytogenetics in AML

- Favorable outcomes
  - t(8;21), t(15;17), inversion 16
  - t(8;21) and inv16 involve AML1-CBFb
- Adverse outcomes:
  - -5,-7, 11q23, trisomies 8 and 13, 6;9 translocation
- Cytogenetic abnormalities have the most significant impact on prognosis and are used to guide therapy
- Gene Mutations:
  - FTL3-adverse
  - NPM1-favorable

Treatment of AML

- Goal: Reduce myeloblasts from $10^{12}$ cells to $10^9$ cells at remission
- Induction Therapy- anthracycline and Ara-C.
  - Complete remission rate 60%-80%. Complete remission lower in older adults
- Consolidation therapy- chemotherapy or BMT
  - High dose Ara-C most commonly used
  - randomized trial has shown no significant difference in overall survival between consolidation chemotherapy, allogeneic BMT, and autologous BMT
Consolidation therapy for AML

Randomized trial comparing chemotherapy with autologous and allogeneic BMT

From Zittoun et al., NEJM 1995

Risk Adapted Therapy for AML

1st complete remission

- Favorable cytogenetics - t(8;21), t(15;17) and inv16
  - chemotherapy

- Unfavorable cytogenetics- t(9;22), -7, -5, 11q23
  - Allogeneic BMT

- Intermediate risk- normal cytogenetics
  - chemotherapy or BMT
  - Meta analysis favors BMT

APML - M3
t(15;17)

- Low WBC and complications of DIC
- All trans-retinoic acid (Atra) is combined with induction therapy
- Atra reduces the complications associated with DIC
- Atra improves complete remission rate
- Arsenic trioxide is used to treat relapsed patients

Issues in AML

Hyperleukocytosis

- associated with very high blast count
- manifestations can include respiratory compromise and/or altered mental status
- medical emergency
- treatment:
  - IV hydration
  - rapid initiation of chemotherapy
  - leukopheresis
  - radiation therapy

Chronic Myelogenous Leukemia

A myeloproliferative disease characterized by the 9;22 chromosomal translocation

- median age at diagnosis of 53
- sex ratio of 1:1
- increased risk associated with prior radiation exposure
- median survival is approximately 5 years

CML

clinical presentation

- ~50% asymptomatic at presentation
- fatigue (80%)
- weight loss (60%)
- abdominal discomfort (40%)
- easy bruising (35%)
- leukostasis, priapism and thrombosis are rare
Ph Chromosome

- 90% of patients with hematologically acceptable CML have the Ph chromosome
- 5% have a variant of the Ph chromosome
- 5% are Ph chromosome negative
  - 40% of these patients will have the bcr-abl translocation detected by PCR

Imatinib (STI571) Gleevec

- BCR-ABL tyrosine kinase inhibitor inhibits proliferation of bcr-abl containing cells
- oral administration
- minimal side effects
  - nausea (55%), myalgias (49%), edema (60%), rash (32%), diarrhea (29%)

Imatinib vs Interferon/Ara-C

<table>
<thead>
<tr>
<th></th>
<th>Imatinib</th>
<th>Interferon/Ara-C</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major Cytogenetic Response</td>
<td>87%</td>
<td>35%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Complete Cytogenetic Response</td>
<td>76%</td>
<td>14%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Freedom from Progression</td>
<td>97%</td>
<td>92%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Other Treatment Options

Clinical Situations
- Gleevec Resistance
- Advance stages of CML

Treatment Options
- Other inhibitors
  - dasatinib (BMS-354825)
  - nilotinib (AMN 107)
- Allogeneic Stem Cell Transplantation

CML: 1 yr results Upfront Studies

<table>
<thead>
<tr>
<th>Agent</th>
<th>MMR (2yr)</th>
<th>CCyR</th>
<th>Prog</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imatinib 400</td>
<td>22-28% (48%)</td>
<td>66%</td>
<td>4%</td>
<td></td>
</tr>
<tr>
<td>Nilotinib 300-400</td>
<td>43% (87%)</td>
<td>79%</td>
<td>1%</td>
<td>3.5 'v' 9</td>
</tr>
<tr>
<td>Dasatinib 100</td>
<td>46% (N/A)</td>
<td>77%</td>
<td>2%</td>
<td>10 'v' 6</td>
</tr>
</tbody>
</table>

Statistically different than imatinib

Saglio et al, NEJM 2010
Kantarjian et al, NEJM, 2010

Question 1

42 yo female presents with a high white blood cell count (>100K) and found to have ALL. Her cytogenetics return 2 weeks later and she is found to have a 9;22 translocation.

The treatment associated with the best chance of long term survival is:

- Gleevec
- Dasatinib
- Intensive Consolidation Chemotherapy
- Allogeneic Stem Cell Transplantation
Question 2

64 yo physician is found to have an elevated lymphocyte count, HCT and Plts normal. Flow cytometry demonstrates the lymphocytes to be CD20+, CD23+ and CD5+. The patient is followed. After developing anemia, therapy with fludarabine and rituxan is started. He has a partial response and then is treated with CAMPATH. He is on no other medications. The patient develops fevers and is found to have diffuse pulmonary infiltrates on CXR. Differential diagnosis would include:

a) CMV pneumonia
b) PCP pneumonia
c) HSV pneumonia
d) All of the above

Summary

- Cytogenetics predict outcome
- Favorable and unfavorable abnormalities
- Risk adapted approach used to guide therapy
- New approaches using tyrosine kinase inhibitors

Disclosures

Edwin P. Alyea

- None

Selected References