Leukemia Review: Types, Diagnostics, Treatments

Eyal C. Attar, M.D.
Massachusetts General Hospital
Cancer Center
June 25, 2010
Myeloproliferative disorders

- MPD
  - PRV
  - ET
  - MF

- CML

- AML

- MDS
  - RA
  - RARS
  - RAEB I
  - RAEB II

Lymphoproliferative disorders

- CLL

- DLBCL

- Low grade lymphoma

- Myeloma

- Lymphoplasmacytic lymphoma (Waldenstrom's)
Clues a Disorder May Exist

- B symptoms
  - Fevers
  - Night sweats
  - Weight loss
- Low blood counts
  - Fatigue, malaise
  - Bruising
  - Infections
- Abnormally high blood counts
  - Strokes
  - Shortness of breath

Bone Marrow Aspiration and Biopsy
Elements of Bone Marrow Analysis

- Aspirate: The Juice
  - Morphologic analysis: what the cells look like under the microscope
  - Flow cytometry: laser analysis of cells using surface markers
  - Cytogenetics: Chromosome analysis
  - Molecular analysis, Correlatives
- Bone: Architecture

Other Useful Diagnostic Tests

- CT/PET scans
  - Lymph node enlargement
- Ultrasound
  - Spleen enlargement
- Spinal tap
  - Abnormal cells, leukemia
- Skeletal survey
Differences Among MDS/MPDs/Acute Leukemias

<table>
<thead>
<tr>
<th></th>
<th>MPD</th>
<th>MDS</th>
<th>Acute Leukemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood counts</td>
<td>High</td>
<td>Low</td>
<td>Low or high</td>
</tr>
<tr>
<td>Bone marrow cellularity</td>
<td>High</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Dysplasia</td>
<td>Minimal</td>
<td>Major</td>
<td>Minimal</td>
</tr>
<tr>
<td>Terminal Differentiation</td>
<td>Present</td>
<td>Absent</td>
<td>Absent</td>
</tr>
<tr>
<td>Blasts</td>
<td>&lt;20%</td>
<td>&lt;20%</td>
<td>≥20%</td>
</tr>
</tbody>
</table>

Acquired mutations enhance proliferation and promote survival:
- Chronic myeloid leukemia: BCR-ABL
- Hypereosinophilic leukemia: FIP1L1-PDGFRα
- Systemic mastocytosis: KITD861V
- Chronic myelomonocytic leukemia: X-PDGFRβ
- Polycythemia vera: JAK2V617F, JAK2K539L
- Essential thrombocytopenia: JAK2V617F, MPLW515L
- Myelofibrosis: JAK2V617F, MPLW515L
Myeloproliferative disorders

- Clonal hematopoietic disorders
- Proliferation of one of myeloid lineages
  - Granulocytic
  - Erythroid
  - Megakaryocytic
- Relatively normal maturation

History

- Duration of symptoms
- Leukocyte deficiencies
  - sinopulmonary infections
- RBC alterations
  - too much: headaches, plethora
  - too little: fatigue
- Plt alterations
  - too much: erythromelalgia
  - too little: epistaxis, bruising
Laboratory Evaluation

- CBC with differential
- MCV
- Reticulocytes
- Examination of the peripheral blood smear
- Iron studies
  - Fe, TIBC, ferritin
  - $B_{12}$, folate
- Erythropoietin level
- Bone marrow biopsy with cytogenetics and, possibly, FISH

Acquired mutations enhance proliferation and promote survival

Chronic myeloid leukemia  BCR-ABL
CML: Peripheral Blood Smear

CML: Epidemiology

- Comprises 15-20% of adult leukemia
- 1-2 cases/100,000 population
- Median age: 50 years
- Slight male predominance
- Only known risk factor: exposure to ionizing radiation
CML: Clinical Findings

- 20-50% of patients asymptomatic
- LUQ abdominal pain
  - splenomegaly
  - splenic infarct
- Bone pain
  - sternum, pelvis, long bones
- Gouty arthritis

CML: Laboratory Testing

- CBC
  - Leukocytosis
  - Thrombocytosis
  - Basophilia
  - Eosinophilia
- Chemistry
  - Elevated LDH
  - Normal leukocyte alkaline phosphatase (LAP) score
CML: Laboratory Testing

- RT-PCR bcr-abl transcript
  - present in the bone marrow and blood
- Bone marrow aspiration and biopsy
  - hypercellular
  - myeloid predominance
  - left shift
  - hyperplastic megakaryocytes
  - abnormal cytogenetics (9;22)

The Philadelphia Chromosome
Clinical Course: Phases of CML

<table>
<thead>
<tr>
<th>Chronic phase</th>
<th>Advanced phases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Accelerated phase</td>
</tr>
<tr>
<td>Median 4-6 years stabilization</td>
<td>Median duration up to 1 year</td>
</tr>
</tbody>
</table>

CML: Management

- **Chronic phase**
  - Tyrosine kinase inhibitors (TKIs)
    - imatinib, dasatinib, nilotinib
  - Interferon
  - Cytarabine
  - Hydroxyurea, busulfan
- **Accelerated phase**
  - Consider TKI, organize stem cell transplant
CML: Management

- **Blast crisis**
  - Induction chemotherapy with TKI to achieve remission
    - AML
      - Antracycline + cytarabine
    - ALL (p190 BCR-ABL vs p210)
      - 5-drug regimen (cyclophosphamide, daunorubicin, vincristine, prednisone, L-asparaginase)
  - Follow with allogeneic SCT if in remission

Mechanism of Action of Imatinib

![Diagram showing the mechanism of action of Imatinib with Bcr-Abl, ATP, Substrate, Imatinib, and Tyrosine phosphate interactions.](Goldman JM. *Lancet*. 2000;355:1031-1032)
CML: Overall Treatment Scheme

Diagnosis

Young with a well-matched donor
Start Imatinib at 400mg/day

Poor response or Initial response Followed by Loss of response
Good response maintained

Consider for Allograft
Add or substitute Other agents Allo-SCT

Allogeneic SCT
Continue Imatinib indefinitely

Acquired mutations enhance proliferation

Chronic myeloid leukemia
Myelofibrosis

Hypereosinophilic leukemia
FIP1L1-PDGFRA

Systemic mastocytosis
KITD816V

Chronic myelomonocytic leukemia
Myelofibrosis

Polycythemia vera
JAK2V617F

Essential thrombocythemia
JAK2V617F

MPLW515L
## Conclusions

<table>
<thead>
<tr>
<th>Acquired mutations enhance proliferation</th>
<th>Targeted therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic myeloid leukemia</td>
<td>BCR-ABL</td>
</tr>
<tr>
<td>Hypereosinophilic leukemia</td>
<td>FIP1L1-PDGFRα</td>
</tr>
<tr>
<td>Systemic mastocytosis</td>
<td>KITD816V</td>
</tr>
<tr>
<td>Chronic myelomonocytic leukemia</td>
<td>X-PDGFRβ</td>
</tr>
<tr>
<td>Myelofibrosis</td>
<td></td>
</tr>
<tr>
<td>Polycythemia vera</td>
<td></td>
</tr>
<tr>
<td>Essential thrombocythemia</td>
<td></td>
</tr>
<tr>
<td>Myelofibrosis</td>
<td></td>
</tr>
<tr>
<td>JAK2V617F</td>
<td></td>
</tr>
<tr>
<td>JAK2K539L</td>
<td></td>
</tr>
<tr>
<td>MPLW515L</td>
<td></td>
</tr>
</tbody>
</table>

**Myelodysplastic Syndromes**
MDS: Characteristics

- Disease of the elderly
  - median diagnosis age 65-75
- M>F
- Annual incidence: 15,000-30,000/year
- Prevalence: 50,000-100,000
MDS: *de novo* vs. *secondary*

- *de novo* MDS
  - no preceding hematologic abnormality
- *secondary* MDS
  - follows chemotherapy or radiation used to treat other diseases (HL, NHL, carcinoma, rheumatoid arthritis, renal transplantation)
    - 2-3 years after topo II inhibitor therapy (etoposide)
    - balanced translocations of MLL at 11q, overt AML
  - 5-10 years after alkylator therapy
    - involves chromosomes 5 and 7, 11p NUP 98, p53
  - 10-15 years after radiation

MDS: Clinical Signs/Symptoms

- Attributed to cytopenias:
  - Anemia: fatigue, depression
  - Leukopenia: infection
    - leading cause of death in MDS
  - Thrombocytopenia: bruising, bleeding
MDS: Initial Tests

- CBC
  - degree and number of cytopenias*
- MCV, reticulocytes
- Examine peripheral blood smear
- Anemia panel:
  - Fe, TIBC, Ferritin
  - B12, Folate
  - EPO

*component of IPSS

MDS: Additional Tests

- Bone marrow aspiration and biopsy
  - aspirate (or touch preps if dry tap)
    - blast percentage
    - dysplasia
  - biopsy
    - dysplasia
    - ALIP, CD34+
  - cytogenetics
    - abnormal in 40-75% of patients with *de novo*, >80% in secondary
    - trisomy 8, 5q-, 7q-, 20q- most common

*component of IPSS
Peripheral Blood-WBCs

Leukopenia
- 50% of MDS patients
- reduced neutrophils
  - hypogranulation
  - pseudo-Pelger-Huet cells
- circulating myeloblasts

Bone Marrow

Hypercellular Dysplasia
- single or multilineage

Perturbed Fe metabolism
- ringed sideroblasts
International Prognosis Scoring System (IPSS) Score

<table>
<thead>
<tr>
<th>Score</th>
<th>0</th>
<th>0.5</th>
<th>1.0</th>
<th>1.5</th>
<th>2.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>% BM blasts</td>
<td>&lt;5</td>
<td>5-10</td>
<td>-</td>
<td>11-20</td>
<td>21-30</td>
</tr>
<tr>
<td>Karyotype</td>
<td>Good (NL, Y-, 5q-, 20q-)</td>
<td>Intermediate (all others)</td>
<td>Poor (complex, Chr 7)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Cytopenias</td>
<td>0/1</td>
<td>2/3</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>


IPSS Accurately Predicts Prognosis in *de novo* MDS

<table>
<thead>
<tr>
<th>Score</th>
<th>Overall Median Survival, years</th>
<th>Time to 25% of patients tx to AML, years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>0</td>
<td>5.7</td>
</tr>
<tr>
<td>Int-1</td>
<td>0.5-1.0</td>
<td>3.5</td>
</tr>
<tr>
<td>Int-2</td>
<td>1.5-2.0</td>
<td>1.2</td>
</tr>
<tr>
<td>High</td>
<td>2.5-3.5</td>
<td>0.4</td>
</tr>
</tbody>
</table>

Deletion 5q is the Most Common Cytogenetic Abnormality Found in MDS

Chromosomal abnormality involving 5q is present in 20% to 30% of all MDS. Patients who have deletion 5q can be grouped into 3 distinct categories with variable prognoses.

Adapted from Verdelius J. Hematology. 2004. ASH MDS Education Session.

5q Syndrome: Chromosomal Abnormality

\[\text{del}(5)(q13q33)\]
5q- Syndrome

- interstitial deletion 5q
  - region between bands q31-q33 encodes IL-3, IL-4, IL-5, IL-9, GM-CSF, c-fms (M-CSFR), others
- W>M 7:3
- median age at diagnosis: 68
- anemia
  - macrocytosis, marked erythroid dysplasia, >80% transfusion-dependent anemia
- normal or slightly elevated plts
- mild leukopenia
- low risk of transformation to AML (15%)
- Uniquely responsive to Imids
MDS: Treatment Approach

Low and Int-1

- 5q deletion with or without other cytogenetic alterations?
  - Yes
    - Lenalidomide
  - No
    - Serum EPO ≤ 500 mU/ml?
      - Yes
        - Epo ± GCSF Supportive care Clinical trial
      - No
        - ATG ± cyclosporine Lenalidomide Azacitidine Decitabine Supportive care Clinical trial

Int-2 and High or therapy-related

- Intensive therapy candidate?
  - Yes
    - Donor available?
      - Yes
        - Azacitidine Decitabine Supportive care Clinical trial
      - No
        - Allogeneic stem cell transplantation
  - No
    - Intensive therapy Supportive care Clinical trial

Acute Myeloid Leukemia
Myeloblasts

Definition and Features

- Malignant neoplasm of myeloid cells
- Reside within
  - bone marrow
  - blood
  - extramedullary tissues
- Cells lack maturation and function
- Suppression normal hematopoiesis
Important Pathogenesis Questions

- What are the important oncogenes and tumor suppressor genes?
- Are all cells within the leukemia equally able to perpetuate the disease? Is there a leukemia stem cell?
- What is the role of the bone marrow microenvironment?

Pathogenesis

- Two hits:
  - Proliferation
  - Block differentiation
- Hypermethylation
- Chromatin alterations
- Increased stromal adhesion

<table>
<thead>
<tr>
<th>Class</th>
<th>Mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I</td>
<td>RAS</td>
</tr>
<tr>
<td></td>
<td>FLT3R</td>
</tr>
<tr>
<td>Type II</td>
<td>CEBPα</td>
</tr>
<tr>
<td></td>
<td>MLL</td>
</tr>
<tr>
<td></td>
<td>NPM1</td>
</tr>
</tbody>
</table>
Causes

- Ionizing radiation
- Occupational exposures: benzene
- Chemotherapy (0.1% of patients)
  - topoisomerase inhibitors (11q23)
  - alkylating agents (deletions of 5 and 7)
- Antecedent hematologic disorder, MDS
- Viruses
  - Retroviruses in animals
  - T-cell leukemia virus
- Hereditary conditions

Epidemiology

- 11,930 new cases of AML in the United States with 9,040 deaths in 2006
- 2.3 new cases/100,000/year
- 18 new cases/100,000/year > 60 yo
- Median age 70 years
- Adults:
  - 85% AML
  - 15% ALL
Age-specific incidence rates: 1998-2002 (NCI-SEER Program)

Classification

- **FAB (French, American, British)** – older
  - > 30% blasts in bone marrow
  - M0 – M7
- **WHO (World Health Organization)** – newer
  - Need >= 20% in bone marrow or blood
  - Considers cytogenetic and molecular lesions
  - Considers prior diseases and treatments
Classification (WHO 2008)

- Acute myeloid leukemia with recurrent genetic abnormalities
  - AML with t(8;21)(q22;q22); RUNX1-RUNX1T1
  - AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22); CBFB-MYH11
  - AML with t(15;17)(q22;q12); PML-RARA
  - AML with t(9;11)(p22;q23); MLLT3-MLL
  - AML with t(6;9)(p23;q34); DEK-NUP214
  - AML with inv(3)(q21q26.2) or t(3;3)(q21;q26.2); RPN1-EVI1
  - AML (megakaryoblastic) with t(1;22)(p13;q13); RBMY5-MKL1
  - Provisional entity: AML with mutated NPM1
  - Provisional entity: AML with mutated CEBPA

- Acute myeloid leukemia with myelodysplasia-related changes

- Therapy-related myeloid neoplasms

- Acute myeloid leukemia, not otherwise specified (NOS)

- Myeloid sarcoma (syn.: extramedullary myeloid tumor; granulocytic sarcoma; chloroma)

- Myeloid proliferations related to Down syndrome

- Blastic plasmacytoid dendritic cell neoplasm

- Acute leukemias of ambiguous lineage

Initial Workup

- History
  - ? AHD, ? prior chemo/XRT
  - Performance status
  - Assessment of comorbidities

- CBC with differential, chemistries, coagulation profile

- BM bx with flow cytometry, cytogenetics, and molecular testing (FLT3R, NPM1, others)

- Hepatitis testing

- HLA-typing

- Sperm banking

- Echocardiogram

- Central venous access
Treat Urgent Issues First

- Assess the CBC, CXR, EKG, and coagulation panel
  - Transfuse RBCs and platelets
  - Antibiotics
- Correct coagulopathy – if DIC consider ATRA (? APL)
- Hydroxyurea and/or leukapheresis
  - Blasts >50,000/uL and signs of leukostasis

Immunophenotype – Flow Cytometry

- Immature markers
  - 34, 38, 117, 133, HLA-DR
- Granulocytic markers
  - 13, 15, 16, 33, 65, MPO
- Monocytic markers
  - NSA, 11c, 14, 64, lysozyme, 4, 11b, 36
- Megakaryocytic markers
  - 41 (Ilb/Illa), 61 (Ilia), 42 (1b)
- Erythroid markers
  - 235a (glycophorin A)
Relationship of Cytogenetics to Prognosis

Prognostic single-gene markers in CN-AML

<table>
<thead>
<tr>
<th>Gene Alteration</th>
<th>Gene Location</th>
<th>Prognostic Impact</th>
</tr>
</thead>
<tbody>
<tr>
<td>FLT3-ITD</td>
<td>13q12</td>
<td>Adverse</td>
</tr>
<tr>
<td>WT1 mutation</td>
<td>11p13</td>
<td>Adverse</td>
</tr>
<tr>
<td>NPM1 mutation</td>
<td>5q35</td>
<td>Favorable</td>
</tr>
<tr>
<td>CEBPA mutation</td>
<td>19q13.1</td>
<td>Favorable</td>
</tr>
<tr>
<td>BAALC overexpression</td>
<td>8q22.3</td>
<td>Adverse</td>
</tr>
<tr>
<td>ERG overexpression</td>
<td>21q22.3</td>
<td>Adverse</td>
</tr>
<tr>
<td>EVI1 expression</td>
<td>3q26.2</td>
<td>Adverse</td>
</tr>
<tr>
<td>MN1 overexpression</td>
<td>22q21.1</td>
<td>Adverse</td>
</tr>
<tr>
<td>FLT3-TKD</td>
<td>13q12</td>
<td>? Adverse</td>
</tr>
<tr>
<td>MLL-PTD</td>
<td>11q23</td>
<td>? Neutral</td>
</tr>
</tbody>
</table>

Courtesy of Dr. G. Marcucci
Molecular Distribution of Cytogenetically Normal AML

Molecular and Cytogenetic Risk Groups

Table 4. Standardized reporting for correlation of cytogenetic and molecular genetic data in AML with clinical data

<table>
<thead>
<tr>
<th>Genotype group</th>
<th>Subsets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favorable</td>
<td>t(8;21)(q22;q22); RUNX1-RUNX1T1</td>
</tr>
<tr>
<td></td>
<td>inv(16)(p13.1q22) or t(1;16)(p13.1;q22); CBFB-MYH11</td>
</tr>
<tr>
<td></td>
<td>Mutated NPM1 without FLT3-ITD (normal karyotype)</td>
</tr>
<tr>
<td></td>
<td>Mutated CEBPA (normal karyotype)</td>
</tr>
<tr>
<td>Intermediate-I</td>
<td>t(8;21)(q22;q22); MLL-GATA2; MLLT3-MLL</td>
</tr>
<tr>
<td></td>
<td>Mutated NPM1 and FLT3-ITD (normal karyotype)</td>
</tr>
<tr>
<td></td>
<td>Wild-type NPM1 and FLT3-ITD (normal karyotype)</td>
</tr>
<tr>
<td></td>
<td>Wild-type NPM1 without FLT3-ITD (normal karyotype)</td>
</tr>
<tr>
<td>Intermediate-II</td>
<td>t(1;19)(q21;q13.3); MLLT10-MLL</td>
</tr>
<tr>
<td></td>
<td>Cytogenetic abnormalities not classified as favorable or adverse</td>
</tr>
<tr>
<td>Adverse</td>
<td>inv(3)(q21q26.2) or t(3;3)(q21q26.2); RPN1-EVI1</td>
</tr>
<tr>
<td></td>
<td>t(1;19)(p13;q14); MLL-MPML</td>
</tr>
<tr>
<td></td>
<td>t(9;11)(p22;q23); MLL-BRAC1 (11q23.3)</td>
</tr>
<tr>
<td></td>
<td>t(5;11)(q35;q23); -5 or del(5); -7, del(7q); complex karyotype</td>
</tr>
</tbody>
</table>

Principles of Treatment

- Induction: goal is to achieve CR
  - 7 + 3 (7 days CI cytarabine, 3 days of anthracycline)
  - IA (idarubicin and cytarabine)
  - ADE
- Consolidation phase: Continued reduction in disease burden, curative for some patients
  - High-dose cytarabine if < 60 yrs
  - Intermediate-dose cytarabine if > 60 yrs
- Maintenance: unclear if beneficial
- Stem cell transplantation
  - Allogeneic in CR1
  - Autologous or allogeneic in CR2

How Can We Improve Treatment Outcomes?

- Induction:
  - Tyrosine kinase inhibitors
    - Sorafenib, AC220, dasatinib
  - Nucleoside analogues
    - Clofarbine, cladribine
  - Leukocyte priming
    - GCSF
  - Interrupt leukemia-microenvironment interactions
    - Plerixfor
  - Reverse DNA and chromatin alterations
    - Hypomethylating agents, HDACi
  - Immunotherapy:
    - Lenalidomide
    - Proteasome inhibition
    - Bortezomib
- Consolidation
  - Chemotherapy vs. autologous SCT vs. allogeneic SCT
- Maintenance
  - Immune modulation (lenalidomide, IL-2, hypomethylation)
FLT3 Receptor

- FLT3 = Fms-like tyrosine kinase 3
- Single transmembrane domain receptor tyrosine kinase
- Overexpressed in 70-100% of AML
- Cytoplasmic domain triggers:
  - PI3K, SRC family, STAT5
- Leads to proliferation and survival activities
- Mutations
  - ITD: internal tandem duplication, 25% of AML, adverse
  - TKD: tyrosine kinase domain, 5%, prognosis unclear


AML FLT3/ITD is a Predictor of Poor Prognosis

FLT3 Receptor Inhibitors

- PKC 412
- MLN 518
- CEP 701
- sorafenib

CALGB 10603: Prospective Phase III, Double-blinded Randomized Study of Induction and Consolidation +/- Midostaurin in Newly Diagnosed Patients < 60 years with FLT3 mutated AML

Primary endpoint: OS

Study drug (50mg BID) is given on Days 8-21 after each course of chemotherapy, and Days 1-28 of each 28 day maintenance cycle

Courtesy of Dr. Richard Stone
CALGB 10503: Phase II Study of Maintenance Decitabine Following Cytogenetically Risk-Adapted Therapy for Newly Diagnosed Adults < 60

AML < 60: Summary

Diagnose
>= 20% BM or PB blasts

Prognosis
Cytogenetics

Good, including NL cytogenetic with NPM1mut

Intermediate

Bad, including NL cytogenetic with FLT3/ITD

1. Remission Induction
2. Consolidation chemotherapy or allogeneic transplant if matched related donor

1. Remission Induction
2. Allogeneic transplant
AML > 60

- Treatment considerations
  - Quality of life
  - Performance status
- Treatment options
  - Supportive care
    - Growth factors, blood products, antibiotics
  - Low dose chemotherapy agents
  - Induction chemotherapy
  - Allogeneic stem cell transplantation

Age, Performance Status, Induction-related Mortality

<table>
<thead>
<tr>
<th>Mortality within 30 days of initiation of induction</th>
<th>Younger than 56 y</th>
<th>56-65 y</th>
<th>66-75 y</th>
<th>Older than 75 y</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. patients</td>
<td>364</td>
<td>242</td>
<td>270</td>
<td>79</td>
</tr>
<tr>
<td>Early deaths* by performance status, no./no. total patients (%)</td>
<td>3/129 (2)</td>
<td>6/72 (11)</td>
<td>9/73 (12)</td>
<td>2/14 (14)</td>
</tr>
<tr>
<td>0</td>
<td>6/180 (3)</td>
<td>6/112 (5)</td>
<td>20/128 (16)</td>
<td>7/40 (18)</td>
</tr>
<tr>
<td>1</td>
<td>1/46 (2)</td>
<td>5/34 (18)</td>
<td>16/52 (31)</td>
<td>7/14 (50)</td>
</tr>
<tr>
<td>2</td>
<td>0/9 (0)</td>
<td>7/24 (29)</td>
<td>9/13 (47)</td>
<td>9/11 (52)</td>
</tr>
</tbody>
</table>

Patients with known pre-study performance status are included.
*Within 30 days of registration to the trial.

Appelbaum. Blood 2006
### Age-related CR Rate: CALGB Study 8923

<table>
<thead>
<tr>
<th>Age</th>
<th>N</th>
<th>CR</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>60-64</td>
<td>98</td>
<td>61</td>
<td>(62%)</td>
</tr>
<tr>
<td>65-69</td>
<td>111</td>
<td>53</td>
<td>(48%)</td>
</tr>
<tr>
<td>70-74</td>
<td>95</td>
<td>52</td>
<td>(55%)</td>
</tr>
<tr>
<td>75-79</td>
<td>59</td>
<td>30</td>
<td>(51%)</td>
</tr>
<tr>
<td>80+</td>
<td>16</td>
<td>5</td>
<td>(31%)</td>
</tr>
</tbody>
</table>

CALGB Memorandum 1995

### CALGB 10502: Phase II/I Study of Bortezomib with Daunorubicin and Cytarabine for Adults with AML Ages 60-75

- **DNR**: Ara-C
- **Bortezomib**: 1.3 mg/m²
- **Int-Ara-C Bortezomib X mg/m²**: D1, 4, 8, 11
- **Int-Ara-C Bortezomib X mg/m²**: D1, 4, 8, 11
- **X**: 0.7, 1.0, 1.3 mg/m²
Epigenetics in Myeloid Malignancies

Hypermethylation

- Hypermethylation leads to gene silencing
  - Methyl-binding proteins inhibit binding of transcription factors
- Results in loss of transcription of tumor suppressor genes and cyclin-dependent kinase inhibitors


Cytosine Nucleoside Analogs

- 2'-Deoxycytidine
- Decitabine
- ara-C
- Cytidine
- 5-azacytidine
AZA-001 Phase III Survival Study Schema

AZA-C 75 mg/m² x 7 days every 28 days (N = 179)

Stratify (FAB, IPSS)

(N = 358)

Eligibility

- RAEB, RAEB-T, CMML
- 10%-29% blasts
- IPSS int-2/high risk

Treatment until disease progression (N = 179)

CCR

1. BSC only (n = 105)
2. Low-dose AraC (n = 49)
3. Induction/consolidation (n = 25)

Primary end point: Overall survival
Secondary end points: IWG CR, PR, HI

Fenaux et al., Lancet Oncol, 2009

Survival in RAEB-T, Azacitidine vs. BSC

Fenaux et al., JCO, 2010

40 35 30 25 20 15 10 5 0

No. of patients at risk

Azacitidine 55 43 38 26 15 10 4 1 0
CCR 58 43 36 22 6 3 0 0 0

Time Since Random Assignment (months)

Patient Survival (proportion)
AML > 60: Summary

Diagnosis

1. Performance status
2. Comorbid Conditions
3. Age
4. Cytogenetics

Good Cytogenetics
1. Remission Induction
2. Consolidation chemotherapy

Non-good Cytogenetics
1. Remission Induction
2. Allogeneic transplant

Patient Transplantable

Non-good Cytogenetics
1. Non-good Cytogenetics
2. Patient Not Transplantable

Supportive care
1. Hypomethylating agent

Transplantation

- Autologous
  - CR1: Probably not beneficial over consolidation chemotherapy
  - CR2: An option for patients without allogeneic donors
- Allogeneic: high risk CR1, all CR2
  - Full (myeloablative)
    - < 61 yo from related donor
    - < 56 yo from unrelated donor
  - Mini (non-myeloablative), RIC (reduced-intensity conditioning)
    - <61 with comorbidities
    - 61-75: related or unrelated donors

- Autologous
  - CR1: Probably not beneficial over consolidation chemotherapy
  - CR2: An option for patients without allogeneic donors
- Allogeneic: high risk CR1, all CR2
  - Full (myeloablative)
    - < 61 yo from related donor
    - < 56 yo from unrelated donor
  - Mini (non-myeloablative), RIC (reduced-intensity conditioning)
    - <61 with comorbidities
    - 61-75: related or unrelated donors
Acute Promyelocytic Leukemia

- 10% of AML
- FAB-M3
- Cytogenetics: t(15;17)
- Younger age
- Pancytopenia
- DIC

Promyeloblasts
S0521: A randomized trial of maintenance versus observation for patients with previously untreated low and intermediate risk acute promyelocytic leukemia (APL)

S0521: A randomized trial of maintenance versus observation for patients with previously untreated low and intermediate risk acute promyelocytic leukemia (APL)

PCR -

R A D A R 6-MP

PCR +

OBS

PCR +

Gemtuzumab

ATRA DNR ATRA DNR

Ara-C AsO₃ AsO₃

CR X₂ CR X₂ CR X₂

SWOG: A Phase II Study of ATRA, AsO₃, and Gemtuzumab in High-Risk APML

SWOG: A Phase II Study of ATRA, AsO₃, and Gemtuzumab in High-Risk APML

PCR -

R A D A R 6-MP

PCR +

OBS

PCR +

Gemtuzumab

ATRA DNR ATRA DNR

Ara-C AsO₃ AsO₃

CR X₂ CR X₂ CR X₂

ATRA Gemtuzumab ATRA Gemtuzumab ATRA Gemtuzumab

AsO₃ AsO₃ AsO₃

6-MP MTX MTX
Summary

- Suspected APL requires immediate care
- Assess for DIC and treat accordingly
- ATRA is a critical component of therapy
- Stratify low vs. high risk
- Excellent survival: 80%

Chronic Lymphocytic Leukemia
CLL

Definition

- Clonal B cell malignancy
- Progressive accumulation of long lived mature lymphocytes
- Increase in anti-apoptotic protein bcl-2
- Intermediate stage between pre-B and mature B-cell
Epidemiology

- Most common leukemia of Western world
- Less frequent in Asia and Latin America
- Male to female ratio is 2:1
- Median age at diagnosis is 65-70 years
- In US population, incidence is similar in different races
- High familial risk with 2-7 fold higher risk

Clinical Features

- Disease of elderly with wide spectrum of clinical features
- 20% are asymptomatic
- Classic B symptoms
- Variable physical findings with normal to diffuse LAD, HSM
Diagnostic Criteria

- Defined by NCI & IWCLL
- Persistent lymphocytosis
- Absolute lymphocyte count exceeding 5000/uL
- Mature appearing B-cells with <10% of prolymphocytes
- CD5+23+ by flow

Blood 1996; 87: 4990

Staging: Rai and Binet staging systems for CLL

<table>
<thead>
<tr>
<th>Stage</th>
<th>Value</th>
<th>Rai</th>
<th>Binet</th>
<th>Median survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Lymphocytosis (≥15,000/mm³)</td>
<td>0</td>
<td>-</td>
<td>150 months (12.5 years)</td>
</tr>
<tr>
<td>II</td>
<td>Lymphocytosis plus nodal involvement</td>
<td>I</td>
<td>&lt;3 node groups</td>
<td>101-108 months (8.5-9 years)</td>
</tr>
<tr>
<td>III</td>
<td>Lymphocytosis plus organomegaly</td>
<td>II</td>
<td>&gt;3 node groups</td>
<td>60-71 months (5-6 years)</td>
</tr>
<tr>
<td>IV</td>
<td>Anemia (RBCs)</td>
<td>III</td>
<td>Hgb &lt;11 g/dL</td>
<td>19-24 months (1.5-2 years)</td>
</tr>
<tr>
<td></td>
<td>Lymphocytosis plus thrombocytopenia (platelets)</td>
<td>IV</td>
<td>PLT &lt;100,000/mm³</td>
<td></td>
</tr>
</tbody>
</table>

## Genetic abnormalities in CLL

<table>
<thead>
<tr>
<th>Genetic abnormality</th>
<th>Incidence (%)</th>
<th>Median survival (months)</th>
<th>Clinical correlation</th>
</tr>
</thead>
<tbody>
<tr>
<td>13q14</td>
<td>55-62</td>
<td>133-292</td>
<td>Typical morphology</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Mutated V&lt;sub&gt;h&lt;/sub&gt; genes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Stable disease</td>
</tr>
<tr>
<td>+12</td>
<td>16-30</td>
<td>114-122</td>
<td>Atypical morphology</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Progressive disease</td>
</tr>
<tr>
<td>del 11q23</td>
<td>18</td>
<td>79-117</td>
<td>Bulky lymphadenopathy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Unmutated V&lt;sub&gt;h&lt;/sub&gt; genes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Progressive disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Early relapse</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>post autograft</td>
</tr>
<tr>
<td>p53 loss/mutation</td>
<td>7</td>
<td>32-47</td>
<td>Atypical morphology</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Unmutated V&lt;sub&gt;h&lt;/sub&gt; genes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Advanced disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Drug resistance</td>
</tr>
</tbody>
</table>


### Effect of genetic abnormalities on survival

Effects of genetic abnormalities on survival in patients with CLL (N=325)

![Graph showing the effect of genetic abnormalities on survival](image)

Prognosis: effect of $V_H$ gene mutations on survival

![Graph showing survival rates with and without mutations.]

Median = 117 months

Median = 293 months


Other Disease Characteristics

- Hypogammaglobulinemia seen >50%
- 5-10% have small monoclonal peak
- Positive Coombs’ test in 30%
- Autoimmune hemolytic anemia & thrombocytopenia in <10%
- Richter’s transformation to DLBCL
- Prolymphocytic leukemia
Treatment

- Chlorambucil, CVP, CHOP
- Fludarabine
- Rituximab
- Campath (alemtuzamab)
- Bendamustine
- Treat early vs. wait?
- Allogeneic SCT

Blood 1996; 88 (suppl 1): 141a

Multiple Myeloma
Spectrum of B-Cell Dyscrasias

- MM, solitary plasmacytoma, MGUS
- Waldenstrom’s macroglobulinemia, lymphoplasmacytic lymphoma
- NHL
- Primary amyloidosis
- Cryoglobulinemia

Plasma Cells in MM
Monoclonal Gammopathy of Undetermined Significance (MGUS)

- Monoclonal protein ≤ 3 g/dL in serum or urine without evidence of MM, Waldenstrom’s, amyloidosis, or other lymphoproliferative disorder
- Incidence: up to 2% of individuals ≤ 50 yo
  - < 3 g/L monoclonal Ig, little or no proteinuria
  - <10% monoclonal BM plasma cells
  - No bone lesions, anemia, or hypercalcemia
- Overall 1% progress each year

Multiple Myeloma

- Prevalence
  - 45,000 Americans have MM
- Median age at diagnosis
  - Men, 62 yr (75% > 70 yr)
  - Women, 61 yr (79% > 70 yr)
- Median survival from diagnosis: 33 months
- 16,570 new diagnoses and 11,310 deaths expected in US in 2006
Multiple Myeloma

- Population subgroups
  - Incidence higher in African Americans
  - Slightly more frequent in men than women
  - Remains mostly incurable

Criteria for Diagnosis of MM

- MM (all 3 required)
  - Monoclonal plasma cells in bone marrow 10% and/or presence of biopsy-proven plasmacytoma
  - Monoclonal protein present in serum and/or urine
  - Myeloma-related organ dysfunction (1 or more): Ca > 10.5 mg/L, SCR > 2 mg/dL, HgB < 10 g/dL, lytic bone lesions or osteopenia
Initial Diagnostic Evaluation

- Hx and PE
- Blood
  - CBC with diff
  - BUN, SCr
  - Electrolytes, Ca, albumin
  - Quantitative immunoglobulins
  - SPEP
  - $\beta_2$-microglobulin
- Skeletal Survey

Lytic Bone Lesions
Presenting Features

- M-protein SIU: 97%
- Anemia: 73%
- Lytic Bone Lesions: 66%
- Bone Pain: 58%
- Renal Insufficiency: 19%
- Hypercalcemia: 13%
- Minor or no abnormalities: 11%
- Hepatomegaly: 4%
- Amyloidosis: 4%
- Non-secretory (no SIU M-protein): 3%

Durie-Salmon Staging System

<table>
<thead>
<tr>
<th>Stage</th>
<th>Criteria</th>
<th>Myeloma Cell Mass ($\times 10^{12}$ cells/m$^2$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>All of the following: Hemoglobin $&gt;$10 g/dL</td>
<td>$&lt;$0.6 (low)</td>
</tr>
<tr>
<td></td>
<td>Serum calcium level $&lt;$10.5 mg/dL (normal)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Normal bone or solitary plasmacytoma on x-ray</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Low M-component production rate: IgG $&lt;$3 g/dL; IgA $&lt;$3 g/dL</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bence Jones protein $&lt;$4 g/24 hr</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>Not fitting stage I or III</td>
<td>0.6–1.2 (intermediate)</td>
</tr>
<tr>
<td>III</td>
<td>One or more of the following: Hemoglobin $&lt;$9.5 g/dL</td>
<td>$&gt;$1.2 (high)</td>
</tr>
<tr>
<td></td>
<td>Serum calcium level $&gt;$12 mg/dL</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Advanced lytic bone lesions on x-ray</td>
<td></td>
</tr>
<tr>
<td></td>
<td>High M-component production rate: IgG $&gt;$7 g/dL; IgA $&gt;$6 g/dL</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bence Jones protein $&gt;$12 g/24 hr</td>
<td></td>
</tr>
</tbody>
</table>

Subclassification

- A: Normal renal function (serum creatinine level $<$2.0 mg/dL)
- B: Abnormal renal function (serum creatinine level $\geq$2.0 mg/dL)
International Staging System

<table>
<thead>
<tr>
<th>Stage</th>
<th>Criteria</th>
<th>Median Survival</th>
</tr>
</thead>
</table>
| I     | Serum $\beta_2$M <3.5 mg/L  
      | Serum albumin ≥3.5 g/dL      | 62 mo         |
| II    | Serum $\beta_2$M <3.5 mg/L  
      | Serum albumin <3.5 g/dL      | 44 mo         |
|       | OR       |                 |
|       | Serum $\beta_2$M 3.5 to <5.5 mg/L* |               |
| III   | Serum $\beta_2$M ≥5.5 mg/L   | 29 mo         |

*Irrespective of serum albumin level

Chromosomal Alterations in MM

- IgH translocations (50%), chromosome 14
  - 11q13; cyclin D1 (15-20%)
  - 4p16.3; FGFR3, MMSET (12%)
  - 16q23; c-MAF (5-10%)
  - 8q24; c-MYC (<10%)
  - 6p21; cyclin D3 (5%)
  - 6p25; IRF4 (5%)
  - 20q11; MAFB (5%)
- Chromosome 13q deletion (50% by FISH)
  - Rb tumor suppressor
  - Coexistence with t(4;14)(p16.3;q32)
- Chromosome 1q amplification (45%)
  - Amplification of 1q21 genes in high-risk MM (BCL9, ILR6, CKS1B)
Treatment Strategy for Newly Diagnosed Myeloma


Therapies for Multiple Myeloma

- Primary therapy
  - Melphalan/prednisone (MP)
  - Vincristine/doxorubicin/dexamethasone (VAD)
  - Dexamethasone
  - Thalidomide, Lenalidomide
  - Doxil
  - Bortezomib
- Transplantation: Auto (1 or 2?) vs. Allo
Summary

- Disorder of neoplastic plasma cells
- The bone microenvironment plays a critical role in disease pathogenesis

Treatment
- Conventional chemotherapeutic agents
- IMIDs
- Combinations
- Maintenance
- Stem cell transplantation
- Bone fortifying agents

Thank you

Eyal Attar
- eattar@partners.org
- 617-724-1124