Acute Leukemia Diagnosis

Elizabeth A. Griffiths, MD
Leukemia Service, Department of Medicine
Roswell Park Cancer Institute
SUNY-UB School of Medicine
# 2013 Estimated US Cancer Cases*

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>841,390</td>
<td>843,820</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cancer Site</th>
<th>Men (%)</th>
<th>Women (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>29%</td>
<td>29%</td>
</tr>
<tr>
<td>Lung &amp; bronchus</td>
<td>14%</td>
<td>14%</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>9%</td>
<td>9%</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>7%</td>
<td>6%</td>
</tr>
<tr>
<td>Melanoma of skin</td>
<td>5%</td>
<td>5%</td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>5%</td>
<td>4%</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>4%</td>
<td>4%</td>
</tr>
<tr>
<td>Oral cavity</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>Leukemia</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>Pancreas</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>All Other Sites</td>
<td>18%</td>
<td>20%</td>
</tr>
</tbody>
</table>

*Excludes basal and squamous cell skin cancers and in situ carcinomas except urinary bladder.

Source: American Cancer Society, 2012
2012 Estimated US Cancer Deaths

<table>
<thead>
<tr>
<th>Tumor Site</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung &amp; bronchus</td>
<td>29%</td>
</tr>
<tr>
<td>Prostate</td>
<td>9%</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>9%</td>
</tr>
<tr>
<td>Pancreas</td>
<td>6%</td>
</tr>
<tr>
<td>Liver &amp; intrahepatic bile duct</td>
<td>5%</td>
</tr>
<tr>
<td>Leukemia</td>
<td>4%</td>
</tr>
<tr>
<td>Esophagus</td>
<td>4%</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>3%</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>3%</td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>3%</td>
</tr>
<tr>
<td>All other sites</td>
<td>25%</td>
</tr>
</tbody>
</table>

**Men**
- Total Deaths: 301,820

**Women**
- Total Deaths: 275,370

<table>
<thead>
<tr>
<th>Tumor Site</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung &amp; bronchus</td>
<td>26%</td>
</tr>
<tr>
<td>Breast</td>
<td>14%</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>9%</td>
</tr>
<tr>
<td>Pancreas</td>
<td>7%</td>
</tr>
<tr>
<td>Ovary</td>
<td>6%</td>
</tr>
<tr>
<td>Leukemia</td>
<td>4%</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>3%</td>
</tr>
<tr>
<td>Uterine corpus</td>
<td>3%</td>
</tr>
<tr>
<td>Liver &amp; intrahepatic bile duct</td>
<td>2%</td>
</tr>
<tr>
<td>Brain/other nervous system</td>
<td>2%</td>
</tr>
<tr>
<td>All other sites</td>
<td>24%</td>
</tr>
</tbody>
</table>
Blood cancers are normal blood cells gone “bad”
Types of Blood Cancers

**Myeloid**
Leukemia
  - Acute (AML)
  - Chronic (CML)
Myelodysplasia (MDS)
Myeloproliferative (MPD)
  - Polycythemia vera (PV)
Essenial
  - Thrombocythemia (ET)
Myelofibrosis (MF)

**Lymphoid**
Leukemia
  - Acute (ALL)
  - Chronic (CLL)
Lymphoma
  - Non-Hodgkin (NHL)
  - Hodgkin (HL/HD)
Multiple Myeloma (MM)
Bone marrow sites in adults
Diagnosis of blood cancers

1. Appearance (morphology)
2. Abnormal protein expression (flow cytometry) (histochemistry)
3. Chromosome abnormalities (cytogenetics)
4. Specific gene mutations
Treatments for Blood Cancers

- Cytotoxic chemotherapy
- Stem cell (bone marrow) transplantation
- Biological therapies (some experimental)
  - Receptor tyrosine kinase inhibitors
  - Antibodies
  - Immunomodulating agents
  - Differentiating agents
Leukemia cells express many abnormal receptors which promote growth.
Leukemia cells express many abnormal receptors which promote growth.

Leukemia cell

Many Leukemia cells
Inhibitors of tumor-specific receptors can inhibit leukemia growth.
## Specific kinase receptor inhibitors for different leukemia patients

<table>
<thead>
<tr>
<th>Leukemia</th>
<th>Abnormal receptor</th>
<th>Inhibitor name</th>
</tr>
</thead>
<tbody>
<tr>
<td>AML (FLT-3 mut)</td>
<td>FLT-3</td>
<td>Sorafenib, Midostaurin, AC220, et al.</td>
</tr>
<tr>
<td>AML (IDH mut)</td>
<td>IDH-2</td>
<td>Enasidinib</td>
</tr>
<tr>
<td>ALL (Ph+)</td>
<td>BCR-ABL</td>
<td>Imatinib, Dasatinib (Sprycel), nilotinib (Tasigna)</td>
</tr>
<tr>
<td>CML</td>
<td>BCR-ABL</td>
<td>Imatinib, dasatinib, nilotinib</td>
</tr>
<tr>
<td>CML (resistant)</td>
<td>BCR-ABL T315I mutation</td>
<td>Ponatinib</td>
</tr>
<tr>
<td>Myelofibrosis (MF)</td>
<td>JAK2</td>
<td>Jakafi</td>
</tr>
</tbody>
</table>
Stem Cell Transplantation

Requires compatible donor stem cell source:
- Allogeneic, autologous, syngeneic,
- Marrow vs. blood vs. cord blood cells

Pre-SCT chemotherapy/immunosuppression (termed conditioning) to prepare BM for new stem cells

Evaluation of immunologic consequences
- Graft vs. Host, Graft vs. Leukemia
Autologous Stem Cell Transplant = Means for High dose Chemotherapy

Stem Cells from Self to the Rescue

- Stem cells are collected from patient
- Patient receives chemotherapy or radiation
- Self-donated stem cells are re-infused into patient
Allogeneic Stem Cell Transplant = Immune/Blood System Replacement

Stem Cells from Donor to the Rescue

Patient receives chemotherapy or radiation
Stem cells are collected from donor
Stem cells are infused into patient, where they migrate to bone marrow
Types of Leukemias

- **Myeloid**
  - Acute leukemia (AML)
  - Chronic leukemia (CML)
  - MDS

- **Lymphoid**
  - Acute leukemia (ALL)
  - Chronic leukemia (CLL)

**Acute** = fast growing (days-weeks)
**Chronic** = slow growing (months-years)
Acute leukemias

• “Leukemia is cancer of the white blood cells—cancer in one of its most explosive, violent incarnations......Its pace, its acuity, its breathtaking, inexorable arc of growth forces rapid, often drastic decisions; it is terrifying to experience, terrifying to observe, and terrifying to treat. The body invaded by leukemia is pushed to its brittle physiological limit.....”

Common symptoms of Leukemia

Systemic
- Weight loss
- Fever
- Frequent infections

Psychological
- Fatigue
- Loss of appetite

Lymph nodes
- Swelling

Spleen and/or liver
- Enlargement

Muscular
- Weakness

Skin
- Night sweats
- Easy bleeding and bruising
- Purplish patches or spots

Lungs
- Easy shortness of breath

Bones or joints
- Pain or tenderness
Acute myeloid leukemia (AML)

Immature myeloid blasts
Auer rods (coalesced granules)
Acute Myeloid Leukemia

- 80% of acute leukemia in adults
- 12,000 cases per year
- Median age of AML = 64 years
- Incidence in USA rises by age group

Rates are per 100,000 and are age-adjusted.
Acute myeloid leukemia (AML): Clinical features

- Most common acute leukemia in adults (median age 67 y)

- Projected incidence 19,950 cases in 2016, mortality rate 50%

- Rapidly growing over days-weeks

- Presents with infection, bleeding or bruising, fatigue due to high or low white blood cell counts, low hemoglobin and low platelets

- May arise from prior hematologic disease such as myelodysplasia, myeloproliferative disorders, or prior chemotherapy/radiation for other cancers
Prognostic Factors in AML

- **Disease Biology:**
  - Cytogenetics (Critical!)
  - Gene mutations (*FLT-3, NPM1, CEBPα* mutations)

- **Clinical Features:**
  - Age > 65 years old
  - Performance status
  - Prior hematologic disorder
  - Therapy-related AML
  - High white blood cell count at diagnosis
Risk Categories in AML: European LeukemiaNet Guidelines

**Favorable risk**
- $t(8;21)$, inv(16) or $t(16;16)$ (Core Binding Factor)
- Normal Karyotype, $\text{NPM1}^{\text{mut}} / \text{FLT3-ITD}^{\text{neg}}$
- Normal Karyotype, $\text{CEBPA}^{\text{mut}}$

**Intermediate-I**
- Normal Karyotype, $\text{NPM1}^{\text{mut}} / \text{FLT3-ITD}^{\text{pos}}$
- Normal Karyotype, $\text{NPM1}^{\text{wt}} / \text{FLT3-ITD}^{\text{pos}}$
- Normal Karyotype, $\text{NPM1}^{\text{wt}} / \text{FLT3-ITD}^{\text{neg}}$

**Intermediate-II**
- $t(9;11)(p22;q23); \text{MLLT3-MLL}$
- Cytogenetic abnormalities not classified as favorable or adverse

**Adverse Risk**
- inv(3), $t(6;9)$, $\text{MLL}$ rearranged, $-5$ or del(5q), $-7$, abnl(17p)
- Complex karyotype
Overall Survival by Cytogenetic Group

AML Treatment Goals

**Diagnosis:** stabilize pt, treatment decision (high/low/no go)

**Induction:** achieve CR and normal hematopoiesis

**Post remission:** prevent relapse
- Consolidation chemotherapy
- Allogeneic vs. Autologous stem cell transplantation

**Refractory/relapsed disease:** prolong survival/QOL
- Clinical trials
- Ara-C/anthracycline based re-induction
- Allogeneic vs Autologous SCT
- Supportive care, hospice
Standard AML therapy

- **Induction**: Admission to hospital for inpatient chemotherapy with two drugs: cytarabine (7 days) and anthracycline (3 days); requires a **30 day inpatient stay** for chemo, antibiotics, transfusions until normal blood counts recover.

- **Remission** = absence of leukemia on BM; does not equal cure (disease gone forever).

- All Pts in remission will require **consolidation chemotherapy** (1-4 shorter rounds of chemotherapy) **OR stem cell transplantation** for long term cure.
Survival with Chemotherapy for Patients with AML

A. <60y at Dx
B. <60y at Dx
C. >60y at Dx
D. >60y at Dx
AML: Allogeneic Stem Cell Transplantation

• Need HLA matched donor (sibling vs. unrelated)

• Only cure for many pts (generally <75 yo)
  – High risk leukemia
  – Refractory to initial chemotherapy
  – Relapsed leukemia
  – Second remission after relapse

• Mortality/morbidity with SCT: 25-30%
Risk of Relapse:
Chemotherapy-alone vs. Allo-Transplant for Intermediate/high-risk AML


P<0.0001

57.8%± 6.2% (4ys) (N=74,40 events)

12.0%± 4.6% (4ys) (N=58,6 events)

©2012 by American Society of Hematology
DFS and OS for Int/High risk AML Patients: Chemotherapy vs Allogeneic Transplant

FLT-3 kinase receptor in normal hematopoietic stem cells

FLT-3 kinase activation in hematopoietic cells results in stimulation of myriad downstream (PI3K, ras, Stat) pathways promoting growth.
FLT-3 Mutations in AML

- Result in constitutive activation of FLT3 kinase
- Activation of growth-related signaling pathways
- FLT3 inhibitors (CEP-701, PKC412, MLN518, SU4516) block receptor kinase activity
FLT-3 mutated AML is associated with worse clinical outcomes

<table>
<thead>
<tr>
<th></th>
<th>Frequency</th>
<th>CR Rate*</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITDs</td>
<td>71 (32%)</td>
<td>65%</td>
</tr>
<tr>
<td>Asp835 Mutations</td>
<td>32 (14%)</td>
<td>82%</td>
</tr>
</tbody>
</table>

* vs. 76%

DFS

p = .03

OS

p = .0004

Frohling, et al., Blood 2002;100:4372
FLT-3 inhibitors in mutant FLT3 AML patients

AML cell with FLT3 mutation

Abnormal FLT-3 receptor auto-phosphorylates in the absence of FL

Sorafenib, Midostaurin, Many others...

FLT-3

FLT-3
Upfront FLT3 Inhibition Improves Survival in Pts w/ FLT3\textsuperscript{mut} AML

Stone RM et al. ASH 2015 Annual Meeting. Abst #6
Acute promyelocytic leukemia (APL)

APL is characterized by the malignant proliferation of immature promyelocytes. The blood fills up with these toxin-loaded promyelocytes. Moody, mercurial, and jumpy, the cells of APL can release their poisonous granules on a whim—precipitating massive bleeding or simulating a septic reaction in the body.

Most cancers contain cells that refuse to stop growing. In APL, the cancer cells also refuse to grow up.

Siddartha Mukherjee (The Emperor of Maladies)
Hematopoiesis

Promyelocyte

APL ↔
Acute promyelocytic leukemia (APL)

APL cells contain a translocation between chr 15 & 17 (here seen by FISH)
APL: PML/RAR-alpha Fusion Protein

Balanced Translocation between Chr 15 and 17

Results in a maturation arrest at the promyelocyte stage

Dominant negative to normal PML

APL Therapy: 
Chemotherapy + Differentiation Therapy

- Immature APL cell
- t(15;17)
- Retinoic Acid (ATRA, Vesanoid)
- Arsenic
- Mature normal WBC
Mechanism of Differentiation Therapy

APL: Double Differentiation has Transformed Management and Outcome

Summary

• We still have much to learn

• Better understanding of the underpinning of leukemia have resulted in improved treatments

• Bench to bedside collaborations have improved outcome, but there is still plenty to do!
Questions??

“I’ll tell you, mock jury duty beats cancer testing.”

Email: elizabeth.griffiths@roswellpark.org
Myelodysplastic syndrome (MDS)
Myelodysplastic syndrome (MDS)

- Clonal hematopoietic stem cell diseases characterized by dysplasia and ineffective hematopoiesis in 1+ myeloid lineages
- Pancytopenia
- Infections, bleeding complications
- Transfusion dependence
- Risk of transformation to AML
- Less than 20% immature myeloid blasts in BM
# Prognosis in MDS: R-IPSS

<table>
<thead>
<tr>
<th>Variable</th>
<th>0</th>
<th>0.5</th>
<th>1</th>
<th>1.5</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytogenetics</td>
<td>VG</td>
<td>G</td>
<td>I</td>
<td>P</td>
<td>VP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BM blasts%</td>
<td>≤2</td>
<td>&gt;2-&lt;5</td>
<td>5-10</td>
<td>&gt;10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hg</td>
<td>≥10</td>
<td>8-10</td>
<td>&lt;8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelets</td>
<td>≥100</td>
<td>50-100</td>
<td>&lt;50</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ANC</td>
<td>≥0.8</td>
<td>&lt;0.8</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Group</th>
<th>Cytogenetic Abnormality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very Good</td>
<td>-Y, del(11q)</td>
</tr>
<tr>
<td>Good</td>
<td>NL, del(5q), del( 20q), ≤2 w/del (5q)</td>
</tr>
<tr>
<td>Int</td>
<td>del(7q), +8, +19, i(17q), any other ≤2 clones</td>
</tr>
<tr>
<td>Poor</td>
<td>-7, inv(3)/t(3q)/del(3q), ≥2 w/ -7/del(7q), complex ≤3</td>
</tr>
<tr>
<td>Very Poor</td>
<td>complex&gt; 3 abnormalities</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Score</th>
<th>Survival (y)</th>
<th>25% AML Tx (y)</th>
</tr>
</thead>
<tbody>
<tr>
<td>V. Low</td>
<td>≤1.5</td>
<td>8.8</td>
<td>NR</td>
</tr>
<tr>
<td>Low</td>
<td>&gt;1.5-3</td>
<td>5.3</td>
<td>10.8</td>
</tr>
<tr>
<td>Int</td>
<td>&gt;3-4.5</td>
<td>3.0</td>
<td>3.2</td>
</tr>
<tr>
<td>High</td>
<td>&gt;4.5-6</td>
<td>1.6</td>
<td>1.4</td>
</tr>
<tr>
<td>V. High</td>
<td>&gt;6</td>
<td>0.8</td>
<td>0.73</td>
</tr>
</tbody>
</table>

Mutations are also Prognostic in MDS

Mutational Data is Additive with Clinical Models

Bejar et al. NEJM. 2011;364:2496-506.
Treatment options for MDS

- Supportive care: transfusions, growth factors
- Hypomethylating agents
  - 5-azacytidine
  - Decitabine
- Allogeneic stem cell transplantation
Hypomethylating Agents

CIMP (+) Neuroblastoma Case A

Case B

Case C

Cancer cell

Demethylating agent

Methylated gene

Unmethylated gene
Azacitidine treatment Improves MDS survival

Log-Rank  \( p=0.0001 \)

\( HR = 0.58 \ [95\% \ CI: 0.43, 0.77] \)

Deaths: AZA = 82, CCR = 113

Difference: 9.4 months

Lenalidomide for MDS therapy

Derivative of *thalidomide*, a morning sickness pill associated with birth defects

Effective for therapy of MDS with chromosome 5 abnormality

Inhibits interactions between MDS cells and the local microenvironment
Phase III Study

Three arms, well matched for age, sex, IPSS, transfusion needs, karyotype

205 pts treated
  – Len (2/3) vs placebo (1/3)

Endpoint: RBC TI ≥ 26 weeks
  – reached in 43-56% of Len pts and 6% for placebo

Toxicity: myelosuppression (90%) and DVTs (2-6%)

No survival benefit

Phase III Lenalidomide OS

Substrate specificity of thalidomide analogues.