Acute Myeloid Leukemia: A Patient’s Perspective

Patrick A Hagen, MD, MPH
Cardinal Bernardin Cancer Center
Loyola University Medical Center
Maywood, IL
Overview

1. What is AML?
2. Who gets AML?
   – Epidemiology of AML
3. Why did I or my family member get AML?
   – Known risk factors
4. How do AML patients present?
5. What evaluation is needed when the diagnosis is suspected?
6. What defines risk and prognosis?
7. What is the treatment for AML?
   – Young and or Fit
   – Elderly and or Frail
   – Do I need a Transplant
Acute Myeloid Leukemia (AML)

- The disease lies within the name:
  - Acute: develops rapidly over weeks to months
  - Myeloid: Relating to the bone marrow
  - Leukemia: Coined in the mid-19th century
    - Greek origin:
      - Leukos = white
      - Haima = blood

- AML is a cancer of blood cells
- Most blood cells come from the bone marrow
- In Leukemia, immature blood cells become cancerous
- These cells also prevent the normal blood cells from maturation
  - Real estate problem as well
Epidemiology

- **Number of New Cases and Deaths per 100,000:** The number of new cases of acute myeloid leukemia was 4.3 per 100,000 men and women per year. The number of deaths was 2.8 per 100,000 men and women per year. These rates are age-adjusted and based on 2011-2015 cases and deaths.

- **Lifetime Risk of Developing Cancer:** Approximately 0.5 percent of men and women will be diagnosed with acute myeloid leukemia at some point during their lifetime, based on 2013-2015 data.
# How Common is AML?

<table>
<thead>
<tr>
<th>Common Types of Cancer</th>
<th>Estimated New Cases 2018</th>
<th>Estimated Deaths 2018</th>
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<tbody>
<tr>
<td>1. Breast Cancer (Female)</td>
<td>266,120</td>
<td>40,920</td>
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<tr>
<td>2. Lung and Bronchus Cancer</td>
<td>234,030</td>
<td>154,050</td>
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<tr>
<td>3. Prostate Cancer</td>
<td>164,690</td>
<td>29,430</td>
</tr>
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<td>4. Colorectal Cancer</td>
<td>140,250</td>
<td>50,630</td>
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<tr>
<td>5. Melanoma of the Skin</td>
<td>91,270</td>
<td>9,320</td>
</tr>
<tr>
<td>6. Bladder Cancer</td>
<td>81,190</td>
<td>17,240</td>
</tr>
<tr>
<td>7. Non-Hodgkin Lymphoma</td>
<td>74,680</td>
<td>19,910</td>
</tr>
<tr>
<td>8. Kidney and Renal Pelvis Cancer</td>
<td>65,340</td>
<td>14,970</td>
</tr>
<tr>
<td>9. Uterine Cancer</td>
<td>63,230</td>
<td>11,350</td>
</tr>
<tr>
<td>10. Leukemia</td>
<td>60,300</td>
<td>24,370</td>
</tr>
<tr>
<td><strong>Acute Myeloid Leukemia</strong></td>
<td><strong>19,520</strong></td>
<td><strong>10,670</strong></td>
</tr>
</tbody>
</table>

Acute myeloid leukemia represents 1.1% of all new cancer cases in the U.S.
Who Gets AML?

Number of New Cases per 100,000 Persons by Race/Ethnicity & Sex: Acute Myeloid Leukemia

<table>
<thead>
<tr>
<th>Race/Ethnicity</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Races</td>
<td>5.2</td>
<td>3.6</td>
</tr>
<tr>
<td>White</td>
<td>5.4</td>
<td>3.7</td>
</tr>
<tr>
<td>Black</td>
<td>4.5</td>
<td>3.3</td>
</tr>
<tr>
<td>Asian/Pacific Islander</td>
<td>4.0</td>
<td>3.0</td>
</tr>
<tr>
<td>American Indian/Alaska Native</td>
<td>3.1</td>
<td>1.8</td>
</tr>
<tr>
<td>Hispanic</td>
<td>4.1</td>
<td>3.1</td>
</tr>
<tr>
<td>Non-Hispanic</td>
<td>5.3</td>
<td>3.7</td>
</tr>
</tbody>
</table>
Percent of New Cases by Age Group

Acute myeloid leukemia is most frequently diagnosed among people aged 65-74.

Median Age At Diagnosis

68
Risk Factors for Developing AML

- Old Age
- Male
- Previous exposure to radiation
  - Radiation treatment for a previous cancer
  - Low level radiation such as that from CT scans or x-rays is controversial and not well defined
- Previous chemotherapy drugs used to treat previous cancers:
  - ~8 years after chemo preceding by MDS often
  - ~1-3 years after chemo without preceding MDS
- Environmental factors:
  - The only proven lifestyle-related risk factor for AML is smoking
  - Certain chemical exposures:
    - Benzene:
      - solvent used in the rubber industry, oil refineries, chemical plants, shoe manufacturing, and gasoline-related industries
    - Formaldehyde:
      - some studies have linked heavy workplace exposure to formaldehyde with AML risk, but this link has not been seen in some other studies.
Risk Factors for Developing AML

- Certain Blood disorders:
  - Chronic Myeloid Leukemia, Polycythemia Vera
  - Essential Thrombocyosis, Primary or Secondary Myelofibrosis
  - Myelodysplastic syndrome

- Chromosome Problems present at birth:
  - Down's syndrome (born with an extra copy of chromosome 21)
  - Trisomy 8 (born with an extra copy of chromosome 8)

- Genetic Syndromes:
  - Fanconi anemia
  - Bloom syndrome
  - Ataxia telangectasia
  - Diamond-Blackfan anemia
  - Schwachman-Diamond Syndrome
  - Li-Fraumeni syndrome
  - Neurofibromatosis type 1
  - Severe Congenital neutropenia (Kostmann syndrome)

Overall this is unfortunately a disease of bad luck and ageing
Development of AML

• Complex process
• Like other human cancers, AML develops as a consequence of many mutations over time
  – Recent studies have revealed that AML develops from a series of genetic mutations within the hematopoietic stem cell
• Epidemiologic and genotypic data have shown that many AML cells have more than once recurring mutation
• Data from animal models of leukemia strongly support a multistep pathogenesis of the disease.
A Clonal Process:

• Utilizing specialized genetic tests at both diagnosis and relapse, we now understand that a phenomenon called “clonal evolution” occurs:
  – Essentially like multiple leukemias at once due to their different responses to treatment
    • Founding clones
    • Novel subclones
    • Clones that develop due to “treatment pressure”

• Although the cytogenetic heterogeneity of AML has been recognized for more than 30 years, the enormous molecular heterogeneity of the disease has become increasingly apparent over the past 15 years.
  – The prognostic importance of this biologic heterogeneity is well accepted,
  – But translation of this new information into improved therapy is just beginning

• Ultimately, this leads to a clonal proliferation of myeloid precursors with a reduced capacity to differentiate into more mature cellular elements.
  – Accumulation of leukemic blasts or immature forms in the bone marrow, peripheral blood, and occasionally in other tissues
  – Variable reduction in the production of normal red blood cells, platelets, and mature granulocytes
Presentation:

- Signs and symptoms related to pancytopenia:
  - Pancytopenia: low blood counts in all 3 cell lines

<table>
<thead>
<tr>
<th>Blood Cell</th>
<th>Function</th>
<th>Symptom when not functioning</th>
</tr>
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<tbody>
<tr>
<td>Red Blood Cell</td>
<td>• Carries oxygen to all organs in the body (heart, lung, kidneys, etc)</td>
<td>• Fatigue</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Weakness</td>
</tr>
<tr>
<td>White Blood Cell</td>
<td>• Responds to inflammation • Organizes the immune system • Fights off infection</td>
<td>• Fever</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Infections</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Kidney complications</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Confusion</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Chest pain</td>
</tr>
<tr>
<td>Platelets</td>
<td>• Establishes balance between bleeding and clotting</td>
<td>• Bleeding: nose, gum</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Bruising</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Rash</td>
</tr>
</tbody>
</table>
Presentation:

- General fatigue is present in the majority of patients and often precedes the diagnosis for a number of months.
- Pallor and weakness are common and attributed to the anemia.
- Bone pain is infrequent in adults with AML,
- Leukemia tumors: myeloid sarcoma or chloroma
- Work-up:
  - Complications related to high white blood cell count:
    - Metabolic abnormalities
    - Coagulation abnormalities
    - “Sluggish Blood”
- Difficult to precisely date the onset of AML: different symptomatic thresholds for choosing to seek medical attention.
  - It is likely that most patients have had more subtle evidence of bone marrow involvement for weeks, or perhaps months, before diagnosis.
Evaluation of a Patient with Suspected AML

- History and Physical Examination
- Complete blood counts: differential and platelet,
- Metabolic studies: CMP, uric acid, DIC panel
- Pregnancy test
- Bone marrow aspirate and biopsy/ Flow cytometry
  - Rule out other disease processes: lymphoma, infections, etc
  - Cytogenetic and FISH studies
  - Morphology studies: what does the bone marrow look like, how many leukemia cells are present
  - Molecular studies:
    - FLT3, NPM1, c-kit, CEBPα, IDH1, IDH2, k-RAS, n-RAS
- HLA typing and eligibility for stem cell transplant
- Serologies: hepatitis, HIV, CMV
- Organ evaluation: ultrasound (echocardiogram) or the heart
Outcomes

• Although it was incurable 50 years ago,
  – It is now cured in 35-40% of adult patients who are 60 years of age or younger
  – It is now cured in 5-15% of patients who are older than 60 years of age

• The outcome in older patients who are unable to receive intensive chemotherapy without unacceptable side effects remains poor, with a median survival of only 5 to 10 months
Risk and Prognosis

SEER 9 5-Year Relative Survival Percent from 1975-2010, All Races, Both Sexes.
Risk: what defines it

• Traditionally:
  – Age, Performance status (how fit are you), white blood cell count, development of AML from a previous blood/bone-marrow disorder

• 1980s-1990s: Cytogenetics started dictating

• 1990s-2010s: Molecular studies
  – FLT3, MLL, NPM1, CEBPα, IDH, TET, c-KIT

• Modern day: next generation sequencing
## 2017 European Leukemia Net Risk Stratification

### Table 5. 2017 ELN risk stratification by genetics

<table>
<thead>
<tr>
<th>Risk category*</th>
<th>Genetic abnormality</th>
</tr>
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<tbody>
<tr>
<td>FAVORABLE</td>
<td>t(8;21)(q22;q22.1); RUNX1-RUNX1T1</td>
</tr>
<tr>
<td></td>
<td>inv(16)(p13.1q22) or t(16;16)(p13.1;q22); CBFB-MYH11</td>
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<tr>
<td></td>
<td>Mutated NPM1 without FLT3-ITD or with FLT3-ITD&lt;sup&gt;low&lt;/sup&gt;†</td>
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<tr>
<td></td>
<td>Biallelic mutated CEBPA</td>
</tr>
<tr>
<td>INTERMEDIATE</td>
<td>Mutated NPM1 and FLT3-ITD&lt;sup&gt;high&lt;/sup&gt;†</td>
</tr>
<tr>
<td></td>
<td>Wild-type NPM1 without FLT3-ITD or with FLT3-ITD&lt;sup&gt;low&lt;/sup&gt;† (without adverse-risk genetic lesions)</td>
</tr>
<tr>
<td></td>
<td>t(9;11)(p21.3;q23.3); MLLT3-KMT2A‡</td>
</tr>
<tr>
<td></td>
<td>Cytogenetic abnormalities not classified as favorable or adverse</td>
</tr>
<tr>
<td>ADVERSE</td>
<td>t(6;9)(p23;q34.1); DEK-NUP214</td>
</tr>
<tr>
<td></td>
<td>t(v;11q23.3); KMT2A rearranged</td>
</tr>
<tr>
<td></td>
<td>t(9;22)(q34.1;q11.2); BCR-ABL1</td>
</tr>
<tr>
<td></td>
<td>inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); GATA2,MECOM(EVI1) −5 or del(5q); −7; −17/abn(17p)</td>
</tr>
<tr>
<td></td>
<td>Complex karyotype,§ monosomal karyotype¶</td>
</tr>
<tr>
<td></td>
<td>Wild-type NPM1 and FLT3-ITD&lt;sup&gt;high&lt;/sup&gt;†</td>
</tr>
<tr>
<td></td>
<td>Mutated RUNX1¶</td>
</tr>
<tr>
<td></td>
<td>Mutated ASXL1¶</td>
</tr>
<tr>
<td></td>
<td>Mutated TP53#</td>
</tr>
</tbody>
</table>
Risk Predicts Survival:

5 Year Overall Survival:
- Favorable: 59.1%
- Intermediate: 32.6%
- Adverse: 22.6%
Current AML Therapy: Younger Adults

- **Induction**: generally a combination of intensive chemotherapy
  - “7 + 3”
  - Dauno 60-90 mg/m²/d x 3d + ara-C 100/200 mg/m²/d x 7d CI.

- **Consolidation**:
  - high- or intermediate-dose ara-C (1-4 cycles)

- **Allogeneic HCT**:
  - Usually recommended for intermediate and high-risk

- **Clinical Trials are critical…..we must do better!**
Current AML Therapy Older Adults

- **Decision**: chemotherapy vs. hypomethylating agent
  - Slow or gentle induction:
  - Hypomethylating agents: Azacitadine and Decitabine

- **Intensive Chemotherapy**: a challenge to figure out who is “fit”
  - **Induction**: dauno 60-90 mg/m2/d x 3d + ara-C 100 mg/m2/d x 7d
  - **Consolidation**: intermediate-dose ara-C (1-4 cycles); no clear role in older adults

- **Low dose Chemotherapy**

- **Reduced intensity HSCT**

- **Clinical Trials are critical.....we must do better!**
Transplant

- Relapse is the enemy!

<table>
<thead>
<tr>
<th>AML risk group†</th>
<th>AML risk assessment criteria at diagnosis</th>
<th>Risk of relapse following consolidation approach</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Chemotherapy or autoHSCT (%)</td>
</tr>
<tr>
<td>Good</td>
<td>−t(8;21) or AML1-ETO, WBC &lt;20</td>
<td>35-40</td>
</tr>
<tr>
<td></td>
<td>−inv16/t(16;16) or CBF3-MYH11</td>
<td></td>
</tr>
<tr>
<td></td>
<td>−CEBPA-biallelic mutant-positive</td>
<td></td>
</tr>
<tr>
<td></td>
<td>−FLT3-ITD-negative/NMP1-positive</td>
<td></td>
</tr>
<tr>
<td>Intermediate</td>
<td>−CN −X −Y, WBC &lt;100, CRe</td>
<td>50-55</td>
</tr>
<tr>
<td></td>
<td>−t(8;21) or AML1-ETO plus WBC &gt;2 or mutant KIT</td>
<td></td>
</tr>
<tr>
<td>Poor</td>
<td>−CN −X −Y, WBC &lt;100, CRe</td>
<td>70-80</td>
</tr>
<tr>
<td></td>
<td>−t(8;21) or AML1-ETO, WBC &gt;20 and/or mutant KIT</td>
<td></td>
</tr>
<tr>
<td></td>
<td>−CN −X −Y, WBC &lt;100, no CRe</td>
<td></td>
</tr>
<tr>
<td></td>
<td>−CN −X −Y, WBC &gt;100</td>
<td></td>
</tr>
<tr>
<td></td>
<td>−CA, but non-CBF, MK-negative, no abn3q26</td>
<td></td>
</tr>
<tr>
<td>Very poor</td>
<td>−CN −X −Y, WBC &gt;100</td>
<td>&gt;90</td>
</tr>
<tr>
<td></td>
<td>−CA, but non-CBF, MK-negative, no abn3q26, EVI1-negative</td>
<td></td>
</tr>
<tr>
<td></td>
<td>−MK-positive</td>
<td></td>
</tr>
<tr>
<td></td>
<td>−abn3q26</td>
<td></td>
</tr>
<tr>
<td></td>
<td>−Non-CBF, EVI1-positive</td>
<td></td>
</tr>
<tr>
<td></td>
<td>−Non-CBF with mutant p53, or mutant RUNX1, or mutant ASXL1</td>
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<tr>
<td></td>
<td>−or biallelic FLT3-ITD with</td>
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<tr>
<td></td>
<td>−FLT3-ITD:FLT3 WT ratio of &gt;0.6</td>
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On the Horizon: Trying to improve outcomes

• Better Chemotherapy:
  – Vyxeos
  – Improved dosing

• Targeted Therapy:
  – FLT3
  – CD33
  – IDH
  – CAR-T a bi/tri specific targeting?

• More and better donors for transplant:
  – Haplo-transplants
  – Cord Blood Expansion

• Maintenance approaches
Questions?

• Cardinal Bernardin Cancer Center:
• Office: 708-327-3157