Acute Myeloid Leukemia

Vu H. Duong, MD, MS
Assistant Professor of Medicine
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Agenda for the Next Hour

- How Do We Make Blood?
- What is AML?
- Signs/Symptoms, Diagnosis, Assessing Risk
- Treatment of Young, Fit Patients
- The Role of Allogeneic Stem Cell Transplantation
- Treatment of Older, Frail Patients
- Options for Relapsed/Refractory Disease
- Acute Promyelocytic Leukemia
- Future Directions
- Questions
How Do We Make Blood?

**Bone Marrow**
- Soft tissue within bone cavities
- The site of blood cell production:
  - *Red blood cells* - carry oxygen
  - *White blood cells* - fight infections, help healing
  - *Platelets* - help blood clot
- Produces several hundred billion blood cells each day
Changes or mutations can cause normal myeloblasts or lymphoblasts to become cancerous:

- Can grow quickly
- Can divide and make copies of themselves
Acute Myeloid Leukemia

- Most common adult leukemia
- ~20,000 patients diagnosed each year
- Slight male predominance
- Average age at diagnosis: 67 years

<table>
<thead>
<tr>
<th>Estimated New Cases</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>180,890</td>
<td>21%</td>
</tr>
<tr>
<td>Lung &amp; bronchus</td>
<td>117,920</td>
<td>14%</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>70,820</td>
<td>8%</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>58,950</td>
<td>7%</td>
</tr>
<tr>
<td>Melanoma of the skin</td>
<td>46,870</td>
<td>6%</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>40,170</td>
<td>5%</td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>39,650</td>
<td>5%</td>
</tr>
<tr>
<td>Oral cavity &amp; pharynx</td>
<td>34,780</td>
<td>4%</td>
</tr>
<tr>
<td>Leukemia</td>
<td>34,090</td>
<td>4%</td>
</tr>
<tr>
<td>Liver &amp; intrahepatic bile duct</td>
<td>28,410</td>
<td>3%</td>
</tr>
<tr>
<td>All Sites</td>
<td>841,390</td>
<td>100%</td>
</tr>
</tbody>
</table>
Causes and Risk Factors

- Age
- Some types of chemotherapy
- Radiation therapy
- Some genetic diseases
- Tobacco smoke
- Chemical exposure such as benzene
- For most patients, there is no obvious cause
Signs/Symptoms

• Leukemia accumulate in the bone marrow (and sometimes other tissues) and inhibits production of normal, healthy blood cells
• Discovered incidentally – “routine” blood work, or
• Suspected after blood work is drawn due to nonspecific symptoms, including:
  – Fatigue, weakness, shortness of breath (low red blood cells)
  – Fever and/or Infections (low neutrophils)
  – Bleeding/bruising (low platelets)
  – Others: aches/pains, weight loss, night sweats
• Symptoms usually appear/progress fairly quickly (weeks to months)
Diagnosis

Based on blood tests and/or bone marrow biopsy

- Visual confirmation of blasts
- Flow cytometry
- Karyotype/cytogenetics
- Molecular mutations

https://www.healthtap.com/
AML, in most cases, is defined as having at least 20% myeloblasts in the bone marrow or blood.
Flow Cytometry

- Identifies and counts the different blood cell types in a patient blood or marrow sample
  - Tells us which markers/proteins are present on leukemia cells
  - Tells us what type of leukemia is present
- Can be completed fairly quickly
AML karyotypes

Normal

- The MOST important pre-treatment predictor of:
  - response to chemotherapy
  - value of stem cell transplant if remission is achieved, and
  - chances of being cured

Complex
Mutations in AML

Patel et al. NEJM 2012

The Cancer Genome Atlas Research Network. NEJM 2013
## Risk Assessment

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Genetic Abnormality</th>
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<tbody>
<tr>
<td>Favorable</td>
<td>t(8;21)(q22;q22.1)</td>
</tr>
<tr>
<td></td>
<td>inv(16)(p13.1q22)</td>
</tr>
<tr>
<td></td>
<td>or t(16;16)(p13.1;q22)</td>
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<tr>
<td></td>
<td>Mutated NPM1 without FLT3-ITD or with FLT3-ITD&lt;sub&gt;low&lt;/sub&gt;</td>
</tr>
<tr>
<td></td>
<td>Biallelic mutated CEBPA</td>
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<tr>
<td>Intermediate</td>
<td>Mutated NPM1 and FLT3-ITD&lt;sub&gt;high&lt;/sub&gt;</td>
</tr>
<tr>
<td></td>
<td>Wild-type NPM1 without FLT3-ITD or with FLT3-ITD&lt;sub&gt;low&lt;/sub&gt; (without adverse-risk genetic lesions)</td>
</tr>
<tr>
<td></td>
<td>t(9;11)(p21.3;q23.3)</td>
</tr>
<tr>
<td></td>
<td>Cytogenetic abnormalities not classified as favorable or adverse</td>
</tr>
<tr>
<td>Poor/Adverse</td>
<td>t(6;9)(p23;q34.1)</td>
</tr>
<tr>
<td></td>
<td>t(v;11q23.3)</td>
</tr>
<tr>
<td></td>
<td>t(9;22)(q34.1;q11.2)</td>
</tr>
<tr>
<td></td>
<td>inv(3)(q21.3q26.2)</td>
</tr>
<tr>
<td></td>
<td>or t(3;3)(q21.3;q26.2)</td>
</tr>
<tr>
<td></td>
<td>-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;sub&gt;high&lt;/sub&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>
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### Other high-risk features:

- **Age > 65**
- **Prior bone marrow disease (MDS, MPN, aplastic anemia, etc.)**
- **Treatment-related AML more likely to have complex karyotype**
- **Relapsed AML**
AML Subtypes/Classification

• AML with recurrent genetic abnormalities
  – Acute promyelocytic leukemia (AML with *PML-RARA*) is included here
• AML with myelodysplasia-related changes
• Therapy-related myeloid neoplasms
• AML, Not Otherwise Specified
• Myeloid sarcoma
• Myeloid proliferations related to Down syndrome
Treatment of AML – General Principles

• Life-threatening disease: patients usually do not survive long without treatment

• Treatment selection is influenced by a variety of factors:
  – Age/fitness/general health
  – Patient’s values and goals
  – Karyotype
  – Molecular mutations
  – Social factors

• Treatment is usually chemotherapy ± stem cell transplant
  – Surgery and/or radiation are utilized in rare situations, but not as the SOLE treatment modality
Treatment of AML – Initial Treatment for Young, Fit Patients

• Induction chemotherapy ("7+3")
  – 7 days of cytarabine continuous infusion
  – 3 days of anthracycline: idarubicin or daunorubicin

• Usually requires hospitalization for several weeks

• MANY potential side effects and complications

• Goal is complete remission:
  – <5% blasts in the bone marrow, AND
  – Good blood counts
  – Up to ~75% of patients will achieve CR, depending on risk category
Induction in Young, Fit Patients

Confirmed AML

7+3 Induction

Day 14 bone marrow biopsy

Residual Disease

Empty Bone Marrow

Await Blood Count Recovery

Bone marrow biopsy

Complete Remission

Poorest Performance Status

Consider less intensive chemotherapy

Good Performance Status

Re-induction

Relapse
Recent Advancements in Induction Chemotherapy

• Daunorubicin/cytarabine liposome (Vyxeos)

• Optimal 1:5 ratio, encapsulated in a lipid/fat “bubble”

• Higher response rates, longer survival compared to “7+3” in patients age 60-75 with:
  – Newly diagnosed therapy-related AML
  – AML with prior MDS or CMML, or
  – AML with myelodysplasia-related changes

Image source: Jazz Pharmaceuticals
FLT3 Mutations

- **Internal Tandem Duplication (ITD):** 25-30%
  - CR rates not significantly worse, but
  - High relapse risk
  - Poor Prognosis

- **Tyrosine Kinase Domain (TKD):** 5-10%

Litzow MR, Blood 2005 106:3331-3332
Midostaurin

- Oral FLT3 inhibitor
- Randomized phase III study in newly diagnosed patients

18-60 yrs of age with FLT3-mutated (non-APL) AML

Induction* (1-2 cycles)
Daunorubicin (Days 1-3)
Cytarabine (Days 1-7)
Midostaurin (Days 8-21)

Consolidation (up to 4 cycles)
High-dose Cytarabine
Midostaurin

Maintenance (12 cycles)
Midostaurin

Daunorubicin (Days 1-3)
Cytarabine (Days 1-7)
Placebo (Days 8-21)

CR

CR

High-dose Cytarabine
Placebo

Placebo

• Relative reduction in risk of death by 22% vs chemotherapy + placebo
• Benefit seen in both ITD and TKD-mutated patients
• Safety/tolerability similar in both arms
Post-remission Therapy in Young, Fit Patients

Goal: Eliminate leukemia cells that cannot be detected after induction, decrease relapse risk

Complete Remission

High Risk: Relapsed, prior MDS, therapy-related, -5, -7, inv(3), t(11q23), del(17p), -17, complex, FLT3 mutated, etc.

Intermediate Risk: Others, including +8 and normal karyotype

Favorable Risk: t(8;21), inv(16)

Consolidation Chemotherapy: Up to 4 Cycles of High-Dose Cytarabine

Allogeneic Stem Cell Transplant
Stem Cell Transplantation

- Very intense process/procedure
- Usually requires hospitalization for several weeks followed by very frequent appointments after discharge from the hospital
Transplantation – Potential Complications

• Graft Versus Host Disease
  – Skin
  – Gastrointestinal tract
  – Liver
  – Others

• Hepatic Sinusoidal Obstruction
  – Painful/enlarged liver, weight gain, fluid retention, yellow color (jaundice)
  – Can lead to liver failure

• Mucositis

• Infections

Vasconcelos L, An Bras Dermatol 2013
http://diseasespictures.com/mucositis/
Treatment of Older/Less Fit Patients

• “Hypomethylating agents” have become the de-facto standard of care

• General Principles/Properties
  – IV or subcutaneous administration (Aza only)
  – Outpatient therapy, well-tolerated
  – May take several cycles before response is seen
  – Can lead to complete remissions, but NOT curative
  – Therapy should be continued indefinitely, even in patients who respond
Hypomethylation Agents (HMAs)

- Promotor
- Genes

DNMT3a

- Methyl
- Hypermethylation

- X

- Genes
Venetoclax

- Oral BCL-2 inhibitor
- Synergizes with HMAs in animal models
- Response rates approach 70% - appears higher than HMA alone (DiNardo CD, Blood 2019)
- Recently FDA-approved in combination with azacitidine/decitabine (or low-dose cytarabine) in older patients with newly diagnosed AML

Mihalyova J. Exp Hematology 2018
Other Drugs

• Gemtuzumab ozogamicin (Mylotarg)
  – Targets CD33, a marker often present on AML cells
  – Chemotherapy (calicheamicin) is attached and is delivered once the complex is internalized
  – Risk of liver damage (veno-occlusive disease)

• Low-dose cytarabine ± glasdegib
  – Glasdegib: oral smoothened inhibitor
  – Combination improved complete remission rates and survival compared to low-dose cytarabine alone

Godwin CD, Leukemia 2017
Relapsed Disease

• Reinduction chemotherapy or hypomethylating agent-based therapy

• New targeted agents
  – FLT3 mutated: Gilteritinib
  – IDH1 mutated: Ivosidenib
  – IDH2 mutated: Enasidenib

• If feasible, allogeneic stem cell transplantation is warranted
Gilteritinib

- Oral FLT3 inhibitor
- FDA-approval based on response rates seen in the interim analysis of the ADMIRAL trial

relapsed or refractory FLT3-mutated (non-APL) AML

R A N D O M I Z E

Gilteritinib 120 mg daily

Salvage Chemotherapy

Endpoints:
- Overall Survival
- Remission Rates

- Rare reports of prolonged QT interval (can lead to abnormal heart rhythms), inflammation of the pancreas, neurologic issues - posterior reversible encephalopathy syndrome
IDH1 and IDH2 Mutations

Hypomethylation

DNMT3a

Methyl

Promotor

Genes

Promotor

Genes

Hypermethylation

Methyl-OH

Promotor

Genes

TET2

α-KG

isocitrate

IDH 1/2
Enasidenib and Ivosidenib

- ~20% of patients with AML have either a mutation in IDH1 or IDH2
- Oral enasidenib/Ivosidenib can lead to complete remissions, but effect usually is not long-lasting
- “Differentiation syndrome” can occur
Acute Promyelocytic Leukemia

• Subtype of AML

• Patients often present with:
  • low blood counts
  • bruising/bleeding, and/or blood clots (disseminated intravascular coagulopathy)

• Caused by a specific chromosomal abnormality t(15;17)
Acute Promyelocytic Leukemia

• Treatment with all-trans-retinoic acid (oral) and arsenic trioxide (IV) ± chemotherapy

• Usually several months of therapy, sometimes with a maintenance phase of up to 2 years

• Excellent prognosis with very high cure rates
Future Directions

- Induction chemotherapy combinations
- Role of minimal residual disease
- Targeted agents – FLT3, IDH mutations
- Immunotherapy – CAR-T cells, immune checkpoint inhibitors, BiTE and DART antibodies
- Maintenance therapy
- Optimal regimens for older/frail patients
- AND MANY OTHERS!
Active Clinical Trials in AML at UMMC

• Newly diagnosed:
  – Beat AML (unfit for intensive chemotherapy)
  – Phase 1/2 study of Indoximod with 7+3

• Maintenance:
  – Randomized phase II study of nivolumab (PD1 antibody) for patients in CR

• Relapsed/Refractory:
  – Phase 1/2 study of MGC006 (CD123 DART antibody)
  – Phase 1 trial of AMG 176 (Mcl-1 inhibitor)
  – Phase 1 study of LAM-003 (heat shock protein 90 inhibitor)
  – Phase 1b study of venetoclax and dinaciclib (MK7965)
THANKS! QUESTIONS?