Acute Myeloid Leukemia (AML)

David Steensma, MD FACP
Associate Professor of Medicine, Harvard Medical School
Institute Physician, Adult Leukemia Program, Dana-Farber Cancer Institute
Hematologic Oncology Service, Brigham & Women’s Hospital

Definitions and Risk Assessment

Definitions
- AML is a hematological (blood) cancer: "clonal" proliferation of abnormal myeloid precursor cells (a type of immature white blood cells), unable to mature
- These malignant "blasts" accumulate in marrow, blood, and sometimes other tissues
  - ≥20% blasts = acute leukemia
  - In health we have <5% blasts
- These abnormal cells inhibit production of normal cells:
  - Red blood cells
  - Platelets
  - Mature white cells (especially neutrophils / granulocytes)

AML by the numbers
- New US cases each year: ~21,000
- Deaths each year: ~11,000
- Median age: ~67 years

Prognostication in AML
- Who is the patient?
  - Age
  - Medical "co-morbidities" (i.e., other problems)
- Did it evolve out of preceding marrow disease (e.g. myelodysplastic syndromes (MDS))?
  - Not always easy to tell...
- Is it a consequence of therapy for another cancer? ("therapy-related AML")
- What are the biological characteristics?
  - Cytogenetic (chromosome) analysis
  - DNA mutational analysis: FLT3, NPM1, CEBPA, etc

AML survival by patient age
- Klepin et al. J Clin Oncol 2014
Why do older patients with AML have a poorer prognosis?

- Frailer and more commonly have other health problems
- Less favorable and more unfavorable chromosomes (=cytogenetics, karyotype)
- Higher incidence of preceding MDS
- Elevated therapy-related morbidity (=complications) and mortality
- Higher incidence of treatment-resistant disease
- Lower rates and duration of complete remission, and shorter median overall survival
- Less likely to be eligible for allogeneic hematopoietic stem cell transplantation (=bone marrow transplant)

Understanding chromosome abnormalities

Cytogenetics (chromosomes, karyotype)

- **“Good-risk”**
  - Translocation t(15;17): Acute promyelocytic leukemia (APML, APL)
  - T >10%. A different disease
  - t(8;21) and inversion 16.
  - >10%. “Core binding factor” alterations

- **“Poor-Risk”**
  - Chromosome 7 deletion
  - Chromosome 5 deletion
  - t(15;16)
  - Complex (i.e., 3 or more abnormalities)
  - Chromosome 11 translocations at 11q23
  - Chromosome 17p abnormalities

- **“Intermediate”**
  - One or two (non-bad) abnormalities

Prognostically important genes include: NPM1, FLT3, TP53 and CEBPA

European LeukemiaNet (ELN)
Molecular and chromosome risk groups

Outcome by ELN risk group
But AML gets more complex!

>40 different recurrently mutated genes; 8 different major subtypes/pathways

200 Patients: 200 Different Diseases?

Each column represents a patient; each row is a gene; each colored box indicates mutation.

“3&7” or “7+3” – The standard remission induction approach for “fit” patients from 1973-2017

Current Treatment

Complete remission rates with intensive treatment according to age and performance status

Remission rate: 40-75%, depending on age and disease biology
Mortality rate: 10-30%, depending on age and comorbid conditions
Emerging Approaches

2017-2018 Acute Myeloid Leukemia: 5 FDA Approvals!

- **4/28/17: Midostaurin** (Rydapt™; Novartis)
  - For adult patients with newly diagnosed AML who have a FLT3 mutation
  - Companion diagnostic: Invivoscribe LeukoStrat CDx FLT3 mutation assay

- **8/1/17: Enasidenib** (Idhifa™; Agios)
  - For adult patients with relapsed/refractory AML who have an IDH2 mutation
  - Companion diagnostic: Abbott m2000 RealTime IDH2 mutation assay

- **8/3/17: CPX-351** (Vyxeos™; Jazz)
  - For adults with either of two types of AML: newly diagnosed therapy-related AML (t-AML) or AML with myelodysplasia-related changes (AML-MRC)

- **9/1/17: Gemtuzumab ozogamicin** (Mylotarg™; Pfizer)
  - For adults with newly diagnosed AML whose tumors express the CD33 antigen (CD33+), and for treatment of patients 2 years or older with relapsed/refractory CD33+ AML

- **7/20/18: Ivosidenib** (Tibsovo™; Agios)
  - For adult patients with relapsed/refractory AML who have an IDH1 mutation
  - Companion diagnostic: RealTime IDH1 mutation assay

CPX-351 Structure: “Nanoparticle 3&7”

- 100 nm bilamellar liposomes
- 5:1 molar ratio of cytarabine to daunorubicin
- 1 unit = 1.0 mg cytarabine plus 0.44 mg daunorubicin

Source: Celator

CPX-351 Trial Design

Randomized Phase 3 Trial of CPX-351 vs 7+3 in Older Patients with sAML

- Primary Endpoint: Overall Survival
- Eligibility criteria:
  - Previously untreated patients
  - Ages 60-75
  - Able to tolerate intensive therapy
  - PS 0/2

CPX-351

- 100 units/ml IV days 1, 2, 5
- Up to 2 inductions and 2 consolidations

7+3

- Daunorubicin 60 mg/m²
- Cytarabine 100 mg/m²

Source: Celator

CPX-351 Trial Result

Overall Survival Greater in CPX-351 Arm vs 7+3 Arm

Source: Lancet J et al ASCO 2016 annual meeting
Activating FLT3 Mutations in AML Are Frequent

ITD: 25-30%
High relapse, poor prognosis

TKD: 5-10%


ITD: 25-30%
High relapse, poor prognosis

A Phase III Randomized Double-blinded Study Of Chemotherapy +/- Midostaurin (PKC412) In Newly Diagnosed Adults aged 18-60 with FLT3 Mutated Acute Myeloid Leukemia (AML)

RATIFY Trial Schema

Overall Survival (Primary Endpoint)
23% reduced risk of death in the Midostaurin arm

NE: not estimable

Recruitment controlled for FLT3 subtype (TKD, ITD-Low, ITD-High)

Phase 2 Study of Quizartinib in AML:
Response Rate

Clinical Response to Gilteritinib Treatment by FLT3 Mutation or TKI Status

Median duration of response: 12.1 weeks FLT3-ITD(+) & 7.0 weeks FLT3-ITD(-)
75% of FLT3-ITD(+) and 48% of FLT3-ITD(-) patients refractory to their last prior therapy, achieved at least a PR to quizartinib

Levis et al ASH 2015

Clinical Response

<table>
<thead>
<tr>
<th>FLT3 Mutation</th>
<th>TKI Status</th>
<th>Median Duration (weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FLT3-ITD(+)</td>
<td>TKI Naïve</td>
<td>7.0</td>
</tr>
<tr>
<td>FLT3-ITD(+)</td>
<td>TKI Resistant</td>
<td>12.1</td>
</tr>
<tr>
<td>FLT3-ITD(-)</td>
<td>TKI Naïve</td>
<td>48%</td>
</tr>
<tr>
<td>FLT3-ITD(-)</td>
<td>TKI Resistant</td>
<td>46%</td>
</tr>
</tbody>
</table>

280 mg Gilteritinib

Clinically meaningful responses: CRc (CR+CRp+CRi) 45% CRc (CR+CRp+CRi) 45% CRc (CR+CRp+CRi) 45% CRc (CR+CRp+CRi) 45% CRc (CR+CRp+CRi) 45% CRc (CR+CRp+CRi) 45% CRc (CR+CRp+CRi) 45%

Data presented as n (%).

CR, complete remission; CRc, composite complete remission; CRi, complete remission with incomplete hematologic recovery; CRp, complete remission with incomplete platelet recovery; ORR, overall response rate; PR, partial response.
• Mardis et al. NCI 2006: First description of IDH mutations in ~9% of patients with AML, associated with normal cytogenetic status (non-AML).
• Subsequent studies found a larger subset, ~15%, of patients with mutations in the IDH gene.
• IDH proteins, essential to the Krebs Cycle, catalyze the deamination of α-ketoglutarate (α-KG) to α-methylmalonate (α-MM).
• Mutant IDH enzymes catalyze a NADPH-dependent reduction of α-KG to 2-hydroxyglutarate (2-HG).
• This leads to accumulation of 2-HG, a neurotoxic metabolite in IDH mutant tumors.

**Clinical activity of Ivosidenib (AG-120) in R/R AML**

<table>
<thead>
<tr>
<th>Dose Escalation</th>
<th>CR, n (%)</th>
<th>CRi/CRp, n (%)</th>
<th>mCR/MLFS, n (%)</th>
<th>SD, n (%)</th>
<th>PD, n (%)</th>
<th>NE, n (%)</th>
<th>DMR, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>R/R AML n=9</td>
<td>10 (16)</td>
<td>1 (2)</td>
<td>2 (3)</td>
<td>27 (43)</td>
<td>30 (38)</td>
<td>7 (11)</td>
<td>31 (33)</td>
</tr>
<tr>
<td>Overall N=78</td>
<td>14 (19)</td>
<td>2 (2)</td>
<td>4 (5)</td>
<td>33 (43)</td>
<td>36 (46)</td>
<td>10 (13)</td>
<td>39 (38)</td>
</tr>
</tbody>
</table>

**Response to Enasidenib (AG-221) in AML/MDS**

<table>
<thead>
<tr>
<th>Overall Response</th>
<th>AG-221 (n=59)</th>
<th>Venetoclax (n=159)</th>
<th>Azacitidine (n=486)</th>
<th>CC-211 (n=221)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>53 (90%)</td>
<td>51 (33%)</td>
<td>41 (17%)</td>
<td>11 (5%)</td>
</tr>
<tr>
<td>CRi</td>
<td>16 (27%)</td>
<td>17 (11%)</td>
<td>8 (3%)</td>
<td>12 (5%)</td>
</tr>
<tr>
<td>CRp</td>
<td>11 (19%)</td>
<td>10 (6%)</td>
<td>10 (4%)</td>
<td>6 (3%)</td>
</tr>
<tr>
<td>PR</td>
<td>2 (3%)</td>
<td>4 (3%)</td>
<td>2 (1%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>SD</td>
<td>6 (10%)</td>
<td>19 (12%)</td>
<td>10 (4%)</td>
<td>27 (12%)</td>
</tr>
<tr>
<td>PD</td>
<td>1 (1%)</td>
<td>5 (3%)</td>
<td>10 (4%)</td>
<td>34 (15%)</td>
</tr>
<tr>
<td>NE</td>
<td>1 (1%)</td>
<td>8 (5%)</td>
<td>4 (2%)</td>
<td>15 (7%)</td>
</tr>
<tr>
<td>CR/PR/SD/N=247</td>
<td>CR=21 (86%)</td>
<td>CRi=4 (16%)</td>
<td>CRp=2 (8%)</td>
<td>CR=22 (10%)</td>
</tr>
</tbody>
</table>

**“DNA Hypomethylating Agent” (HMA) therapies**

• Less intensive treatment, increasingly used for frail or older patients
• Typically administered in outpatient clinic
• Can lead to therapeutic responses, including transfusion independence, decrease in leukemic burden, and less commonly, complete remissions
• However, responses often transient, with leukemic progression and brief post-HMA survival
• Decitabine and azacitidine FDA approved for MDS (and AML with 20-30% blasts)
• In development: guadecitabine (SGI-110), CC-486 (oral azacitidine), cedazuridine/ASTX727 (oral decitabine + inhibitor of breakdown)

**Hypomethylating agent therapy among older adults with AML**

**Venetoclax: An Oral Selective BCL-2 Inhibitor**

• Venetoclax was shown to synergize with HMA in mouse models, suggesting that combination with HMA may be a promising approach in AML.
• FDA approved for Chronic Lymphocytic Leukemia
• Reported phase 1, open-label, nonrandomized, dose-escalation trial of venetoclax in combination with DEX or AZA in older (>=65 years), treatment-naive AML patients (NCT02650579).
• Ongoing randomized trials in up-front and relapsed/refractory AML.
Venetoclax + HMA Efficacy in AML

<table>
<thead>
<tr>
<th>Overall Response, n (%)</th>
<th>Arm A (VEN + DEC)</th>
<th>Arm B (VEN + AZA)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CR+CRi</strong></td>
<td>3 (50)</td>
<td>9 (75)</td>
<td>12 (35)</td>
</tr>
<tr>
<td><strong>ORR</strong> (CR+CRi+PR)</td>
<td>3 (50)</td>
<td>10 (83)</td>
<td>13 (38)</td>
</tr>
<tr>
<td><strong>CR+CRi+PR+MLFS</strong></td>
<td>3 (50)</td>
<td>11 (92)</td>
<td>14 (41)</td>
</tr>
</tbody>
</table>

- 27/45 (60%) patients achieved CR/CRi, 1/45 (2%) had partial remission (PR), and 4/45 (9%) patients achieved morphologic leukemia free state (MLFS) when treated at all dose levels.
- 23/34 (68%) patients achieved CR/CRi when treated at 400 and 800mg dose levels.
- Median time to CR/CRi was 1 month (range, 0.8–3.8).
- Median duration of response was 8.4 months (95% CI: 6.8–not reached).
- 7/45 (16%) patients experienced morphologic relapse after achieving a CR or CRi.
- Median time on study was 3.2 months (range, 0.2–14.8).


Chimeric Antigen Receptor T (CAR-T) Cells: An Advance for ALL; Will They Be Useful Someday for AML?

- Personalized medicine approach to treating AML.
- Transplant ≈ “Rebooting the System”

Immune Checkpoint Inhibitors: A Breakthrough In Solid Tumors, What About AML?


What’s Next For AML?

- “Personalized” Medicine
- www.leadingwithtrust.com

Stem Cell (Bone Marrow) Transplantation: Rebooting the System
**What Needs To Be Done Before Transplant?**

**Donor Identification**

- Typical Pre-Transplant Testing
  - Electrocardiogram (ECG)
  - Echocardiogram
  - Pulmonary function tests (PFTs, spirometry)
  - Dental exam and cleaning
  - Updated marrow biopsy
  - Blood tests: tissue type, antibodies, blood type, infection markers, organ function

**Allogeneic Hematopoietic Stem Cell Transplant (Allo-HSCT)**

- Source: NCI

**Transplant Trends**

- Older fit patients are increasingly considered eligible (up to ~75 years)
- Increasing use of half-matched “haplo” transplant (usually parent/child)
  - Randomize transplant of haplo vs cord blood
  - Increasing elective use of bone marrow rather than blood stem cells as donor source
  - Requires an operation, but may reduce graft-versus-host (GVH)
- Increasing use of post-transplant preventive or pre-emptive therapy
  - e.g., sorafenib after FLT3 AML allo-SCT
- Monitoring and treatment of graft-versus-host and infection is improving

**Conclusions**

- FDA approval of 5 new AML drugs in 2017-2018!
  - Hopefully the beginning of a wave...
- Biological understanding of AML is improving
- More than 300 AML clinical trials ongoing, testing >40 different novel compounds
  - Clinical trials are the only way to move the field forward
- Transplant is more broadly applied, outcomes improving

**Thank you!**