AML in Adults

Guru Subramanian Guru Murthy MD
Assistant professor, Hematology/Oncology
Medical College of Wisconsin
Background

- Clonal expansion of myeloid blasts in the blood/bone marrow

- A malignancy that affects blood, bone marrow and other tissues
Epidemiology

- About 21450 new cases in 2019 and 10920 deaths
- Median age at diagnosis 67 years
- 54% diagnosed are over 65 years

https://seer.cancer.gov
Etiology and types of AML

**Primary AML**
Causative factors are unclear with possible links to petrochemicals, benzene, pesticides and ionizing radiation

**Secondary AML**
Evolves from prior disorders such as MDS, MPN, CMML

**Therapy related AML**
Prior cancer treatment with chemotherapy or radiation

Acute promyelocytic leukemia is a distinct subtype
How does AML start?

- Series of genetic and molecular events occur in hematopoietic precursor cells
- Most patients have 3 or more somatic alterations with > 100 genomic lesions
- Unclear how much time is needed to acquire these events and progress
- Older patients tend to have more bad mutations
- Age related clonal hematopoiesis

Kronke J et al. Blood 2013
Ley et al. NEJM 2013
What happens in APL?

Clinical presentation

- Bleeding tendencies in APL
- Gum enlargement in certain subtypes of AML
Workup

• Complete blood count
• Peripheral blood smear review
• Bone marrow biopsy
• Cytogenetics/FISH
• Flow cytometry
• Molecular markers

• Electrolytes, liver function test, renal function test
• ECHO or MUGA scan
Chromosomal and molecular abnormalities in clinical context

### European LeukemiaNet Risk Stratification by Genetics in Non-APL AML

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Genetic Abnormality</th>
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| Favorable     | t(8;21)(q22;q22.1); RUNX1-RUNX1T1  
                | inv(16)(p13.1q22) or t(16;16)(p13.1;q22); CBFB-MYH11  
                | Mutated NPM1 without FLT3-ITD or with FLT3-ITD<sup>a</sup>  
                | Biallelic mutated CEBPA |
| Intermediate  | Mutated NPM1 and FLT3-ITD<sup>a</sup>  
                | Wild-type NPM1 without FLT3-ITD or with FLT3-ITD<sup>a</sup> (without adverse-risk genetic lesions)  
                | t(9;11)(p21.3;q23.3); MLLT3-KMT2A  
                | Cytogenetic abnormalities not classified as favorable or adverse |
| Poor/Adverse  | t(6;9)(p23;q34.1); DEK-NUP214  
                | t(v;11q23.3); KMT2A rearranged  
                | t(9;22)(q34.1;q11.2); BCR-ABL1  
                | inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); GATA2,MECOM(EVI1)  
                | -5 or del(5q); -7; -17/abn(17p)  
                | Complex karyotype,§ monosomal karyotype||  
                | Wild-type NPM1 and FLT3-ITD<sup>high</sup>  
                | Mutated RUNX1††  
                | Mutated ASXL1 ††  
                | Mutated 7p53# |
Phases of therapy

- **Induction**
  - Chemotherapy

- **Post remission**
  - Chemotherapy or Allogeneic BMT

Leukemia no longer detectable with tests.
Types of AML – Treatment standpoint

- Newly diagnosed
- Relapsed/refractory
Frontline Therapy decision making

**Intensive therapy**
Involves combination chemotherapy

**Less intensive therapy**
Involves agents such as HMA, venetoclax, IDH1 inhibitors, gemtuzumab
Assessment of fitness to therapy

General
- Karnofsky performance scale
- ECOG performance scale
- Comprehensive geriatric assessment

Comorbidities
- Charlson comorbidity index
- HCT-CI (Sorror)

Composite
- NCCN
- SWOG/MDACC
- MRC/NCRI
- Sorror AML model
- German SAL score
Timeline of AML therapy approval

Abdel-Wahab O. The Hematologist. 2018;15; DAURISMO® PI 2018; RYDAPT® PI 2018; IDHIFA® PI 2017; VYEXOS® PI 2017; MYLOTARG® PI 2018; TIBSOVO® PI 2018; XOSPATA® PI 2018.
INTENSIVE
7+3 regimen

- 7 days of cytarabine IV
- 3 days of daunorubicin or idarubicin IV
- Typically hospitalized for 3-4 weeks
- Risk of infection, bleeding, and other complications
- Induces CR in 70-80% of denovo AML
Gemtuzumab Ozogamicin

- CD33-directed antibody-drug conjugate
- Withdrawn in 2010 – hepatotoxicity with 9mg/m2 dose
- Subsequently proven to have benefits in AML when given in reduced doses
- Newly-diagnosed CD33-positive AML in certain risk groups
- Risk of veno-occlusive disease

Castaigne et al. Lancet 2012
Hills RK et al. Lancet Oncol 2014
Midostaurin

- FLT3 inhibitor
- Newly diagnosed AML with FLT3 mutation (ITD or TKD)
- Tested with daunorubicin 60mg/m2 and cytarabine 200mg/m2 (7+3)
- 50mg BID oral from days 8-21
- Bone marrow day 21
- Continued during consolidation and maintenance
- Side-effects: nausea, skin rash, GI upset

Stone RM et al. NEJM 2017

4-year OS - 51 vs 44%
22% lower risk of death
CPX-351

- Liposomal carrier
- 5:1 molar ratio of cytarabine to daunorubicin
- Approved for newly diagnosed therapy-related AML or AML with myelodysplasia-related changes (AML-MRC)
- Given IV on days 1, 3, 5
- Can be given as outpatient

Lancet JE et al. JCO 2018
LESS INTENSIVE
Hypomethylating Agents (HMA)

- Includes azacitidine and decitabine
- Modest effectiveness as single agent in newly diagnosed AML
- CR rate of 17-20%
- Decitabine - Median OS 7.7 mon
- Azacitidine: Median OS 10.4 mon

Kantrajian et al. JCO 2012
Dombert et al. Blood 2015
Venetoclax with HMA or cytarabine

- BCL2 inhibitor
- Effective when combined with HMA or cytarabine
- Taken orally once a day along with HMA or cytarabine
- CR 54-70%
- Side-effects are minimal, typically low blood counts, risk of tumor lysis syndrome
Glasdegib

- Hedgehog pathway inhibitor
- Oral 100mg daily along with cytarabine 20mg daily x 10 days every 28 days
- CR 17%, OS 8.8 mon
- SE – low blood counts, nausea, fatigue

Cortes J et al. Leukemia 2018
IDH inhibitors
- Inhibits IDH2, a mutation seen in 12% of AML
- Approved as single agent, 100mg daily, oral
- Response rates 40%, CR 19%
- Responses increase with time
- Can cause increase in WBC, differentiation syndrome, elevated bilirubin

Stein E et al. Blood 2018
Ivosidenib

- Inhibits IDH1, a mutation seen in 10% of AML
- Approved as single agent, 100mg daily, oral
- Response rates 40%, CR 20%
- Responses increase with time
- Can cause increase in WBC, differentiation syndrome

DiNardo et al. NEJM 2018
Changing landscape of frontline therapy

- 7+3 or similar regimen
- Decitabine or azacitidine
- Subcutaneous cytarabine

Intense

7+3
7+3+mylotorg
7+3+midostaurin
CPX-351

Less intense

- Venetoclax + Azacitidine or decitabine
- Venetoclax + cytarabine
- Glasdegib + cytarabine
- IDH1/2 inhibitors
Relapsed-Refractory AML

THERAPY FOR RELAPSED/REFRACTORY DISEASE

Clinical trial
Aggressive therapy for appropriate patients:
- Cladribine + cytarabine + granulocyte colony-stimulating factor (G-CSF) ± mitoxantrone or idarubicin
- HiDAC (if not received previously in treatment) ± (idarubicin or daunorubicin or mitoxantrone)
- Fludarabine + cytarabine + G-CSF ± idarubicin
- Etoposide + cytarabine ± mitoxantrone
- Clofarabine ± cytarabine + G-CSF ± idarubicin

Less aggressive therapy:
- Hypomethylating agents (azacitidine or decitabine)
- Low-dose cytarabine (category 2B)

Therapy for AML with FLT3 mutation
- Gilteritinib
- Hypomethylating agents (azacitidine or decitabine) + sorafenib (FLT3-ITD mutation)

Therapy for AML with IDH2 mutation
- Enasidenib

Therapy for AML with IDH1 mutation
- Ivosidenib

Therapy for CD33-positive AML
- Gemtuzumab ozogamicin

NCCN Guidelines for AML, 2019
Allogeneic transplant

Infections

GVHD

Disease relapse
Allogeneic stem cell transplant

- Curative option
- Outcomes are best when done in first CR
- Indicated for poor risk AML and certain groups of intermediate risk AML
- Risk of early and late transplant related complications
- Risk of relapse
APL therapy

• High cure rates – over 90% in clinical trials, and >60-70% in population based studies

• ATRA (oral) and Arsenic (IV) are effective treatments and chemotherapy free

• Risk of early mortality due to bleeding complications and infections

Burnett AK et al. Lancet Oncol 2015
Where we stand..

At a Glance

- Estimated New Cases in 2019: 21,450
- Estimated Deaths in 2019: 10,920
- % of All New Cancer Cases: 1.2%
- % of All Cancer Deaths: 1.8%
- Percent Surviving 5 Years: 28.3%

https://seer.cancer.gov
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<td>Lintuzumab-Ac225 in Combination With CLAG-M Chemotherapy in Patients With Relapsed/Refractory Acute Myeloid Leukemia</td>
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<td>Pracinostat in Combination With Gemtuzumab Ozogamicin (PraGO) in Patients With Relapsed/Refractory Acute Myeloid Leukemia</td>
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<td>Safety, Tolerability, Pharmacokinetics and Efficacy of AMG 397 in Subjects With Multiple Myeloma, NHL, and AML</td>
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<td>A Study of the Safety and Tolerability of ABBV-621 in Participants With Previously Treated Solid Tumors and Hematologic Malignancies</td>
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<td>Safety, Tolerability, Pharmacokinetics, and Efficacy of AZD2811 Nanoparticles as Monotherapy or in Combination in Acute Myeloid Leukemia Patients</td>
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<td>Safety Study of MGD006 in Relapsed/Refractory Acute Myeloid Leukemia (AML) or Intermediate-2/High Risk MDS</td>
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<td>Study of Iomab-B Prior to Hematopoietic Cell Transplant vs. Conventional Care in Older Subjects With Active, Relapsed or Refractory Acute Myeloid Leukemia</td>
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<td>A Phase Ib/II, Multicenter, Single Arm, Open-Label Study, To Evaluate the Safety, Tolerability and Efficacy of the BL-8040 and Atezolizumab Combination for Maintenance Treatment in Subjects With Acute Myeloid Leukemia Who Are 60 Years or Older</td>
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<td>Efficacy and Pharmacogenomics of Salvage CLAG-M Chemotherapy in Patients With Relapse/Refractory and Secondary Acute Myeloid Leukemia</td>
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QUESTIONS ?