Acute Myeloid Leukemia (AML): Finally Making Progress?

Joshua Zeidner, MD
Assistant Professor of Medicine
University of North Carolina
Lineberger Comprehensive Cancer Center

Disclosures

- Honoraria (ended 12/2017): Celgene, Tolero
- Research support: Merck, Takeda Millennium, Tolero

Objectives

- To discuss pathogenesis/etiology of AML
- To discuss diagnostic testing in AML
- To discuss management of AML in both younger & older patient populations highlighting recent drug approvals
- To discuss novel concepts and investigational agents for treatment of AML
Case

- 67 yo M with past medical history significant for Stage I Squamous Cell Carcinoma of Oropharynx in 2015, s/p Cisplatin + XRT, with no evidence of recurrence, presents with progressive fatigue, chest tightness and found to have pancytopenia with WBC = 1.3x10^9/L, Hb = 7.8 g/dL, and platelet count = 69x10^9/L. A bone marrow biopsy is performed revealing 20% blasts by manual aspirate differential with multilineage dysplasia. Cytogenetics reveal a highly complex karyotype and NGS mutational testing reveals TP53 mutation. The patient otherwise has an ECOG PS = 0 and is healthy with minimal other comorbidities.

Question 1

What is the next step in the management of this patient?

A) Refer directly for allogeneic stem cell transplant  
B) 7+3 induction chemotherapy  
C) CPX-351  
D) Azacitidine  
E) 7+3 + Midostaurin

What is AML?

- Clonal proliferation of myeloid precursors (i.e. myeloblasts)
  - Reduced capacity for differentiation
  - Reduced capacity for cell death => uncontrolled proliferation
Pathogenesis of AML

- Stem Cell Hypothesis - AML arises from early hematopoietic progenitor/stem cell
  - Two-Hit Hypothesis
    - Class 1 Mutations
      - Proliferative advantage
        - Ex: FLT3, NPM1, C-KIT
    - Class 2 Mutations
      - Impair hematopoietic diff.
        - Ex: CEBPA

How To Cure AML?

- Holy grail of AML = Cure
- Working hypothesis is that all (or most) AML’s arise from a LSC
- The more primitive LSC - harder to eradicate -> refractory and/or relapse
- Genetic features of AML provide a clue for how primitive AML is
Pathology of AML

- Diagnosis: >20% myeloblasts in PB or BM
  - Blast % irrelevant in CBF AML [t(8;21); inv(16)] and APL
- Morphology: Smooth chromatin, prominent nucleoli, Auer Rods
- Immunophenotype:
  - Myeloid antigens:
    - MPO, CD13, CD33, CD15
  - Monocytic antigens:
    - NSE, CD11c, CD14, CD64, Lysozyme
  - Blast markers:
    - CD34, CD117

Maslak P, ASH Image Bank

Epidemiology of AML

- 18,000 new cases of AML/year
  - > 10,000 deaths/year
- Median age - 67-68 years
  - All ages can be affected

SEER Data, Walter, Leukemia 2015

Clinical Presentation

- Rapid onset of symptoms over 1-7 days, can be more protracted in MDS -> AML

**Diagnosis**

- Bone marrow biopsy and morphology
- If circulating blasts > can make dx by flow cytometry
- Myeloblasts >20% in bone marrow or blood
- Cytogenetics and molecular markers - Critical!

![Bone marrow biopsy image](image)

**Classification/Prognostication**

- FAB Classification outdated (M0-M7)
- Genetic information critical for prognostication
  - It's really all about the chromosomes!
- European LeukemiaNet (2010) - 4 risk groups

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Cytogenetic/ Molecular</th>
<th>Younger pts.</th>
<th>Older pts.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favorable</td>
<td>t(8;21); inv(16); inv(16)</td>
<td>41%</td>
<td>20%</td>
</tr>
<tr>
<td>Intermediate-1</td>
<td>Normal karyotype + FLT3-ITD</td>
<td>18%</td>
<td>19%</td>
</tr>
<tr>
<td>Intermediate-2</td>
<td>t(9;11) and all other abn.</td>
<td>19%</td>
<td>30%</td>
</tr>
<tr>
<td>Adverse</td>
<td>t(6;9); del(5q); -7; abnl(17p); complex</td>
<td>22%</td>
<td>31%</td>
</tr>
</tbody>
</table>

Dohner, Blood 2010; Mrozek, J Clin Oncol 2012

**Do Risk Groups Matter?**

- Risk groups validated to predict outcome

![Graph of overall survival probability](image)

Mrozek, J Clin Oncol 2012
AML is a Heterogeneous Disease

Patel, NEJM 2012

Complexity of Molecular Mutations in AML

Gimwade, Blood 2016

11 Genomic Classes of AML

Papapetrou et al, NEJM 2016
Driver Mutations With Effect on OS

<table>
<thead>
<tr>
<th>Gene</th>
<th>Prognostic</th>
<th>Therapeutic</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASXL1</td>
<td>Poor risk</td>
<td>-</td>
</tr>
<tr>
<td>BCOR</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CEBPA</td>
<td>Favorable</td>
<td>-</td>
</tr>
<tr>
<td>DNMT3A</td>
<td>Most studies: myeloma risk.</td>
<td></td>
</tr>
<tr>
<td>ETV/TEL</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>EZH2</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>FLT3-ITD/TKD</td>
<td>Yes (ITD)</td>
<td>Yes</td>
</tr>
<tr>
<td>IDH1</td>
<td>?</td>
<td>Yes in CBF</td>
</tr>
<tr>
<td>IDH2</td>
<td>?</td>
<td>Yes</td>
</tr>
<tr>
<td>KIT</td>
<td>Yes in CBF</td>
<td>Yes in AML</td>
</tr>
</tbody>
</table>

Gene-gene interactions:

- RUNX1-ASXL1: 5.4 (p = 0.018)
- EZH2-ASXL1: 1.6 (p = 0.044)
- WT1-IDH1: 0.8 (p = 0.0005)
- WT1-IDH2: 0.8 (p = 0.0005)
- WT1-IDH1: 0.8 (p = 0.0005)

Other epigenetic:

- IDH1/2: 1.2 (p = 0.001)
- TET2: 1.2 (p = 0.001)
- JAK2: 1.2 (p = 0.001)
- SF3B1: 1.2 (p = 0.001)

Myeloid Molecular Panel- UNC

<table>
<thead>
<tr>
<th>Gene</th>
<th>Prognostic</th>
<th>Therapeutic</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASXL1</td>
<td>Favorable</td>
<td>-</td>
</tr>
<tr>
<td>BCOR</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CEBPA</td>
<td>Favorable</td>
<td>-</td>
</tr>
<tr>
<td>DNMT3A</td>
<td>Most studies: myeloma risk.</td>
<td></td>
</tr>
<tr>
<td>ETV/TEL</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>EZH2</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>FLT3-ITD/TKD</td>
<td>Yes (ITD)</td>
<td>Yes</td>
</tr>
<tr>
<td>IDH1</td>
<td>?</td>
<td>Yes in CBF</td>
</tr>
<tr>
<td>IDH2</td>
<td>?</td>
<td>Yes</td>
</tr>
<tr>
<td>KIT</td>
<td>Yes in CBF</td>
<td>Yes in AML</td>
</tr>
</tbody>
</table>

AML Outcomes

- Extremely poor prognosis with conventional therapy.
- 5-year survival rates = 40% in <65 yrs and <10% in >65 yrs

5-Year Relative Survival (%) by Age (Years)

- Total
- Males
- Females

Walter Leukemia 2015
AML Outcomes Over Time

- Improvements in survival likely due to supportive care and allogeneic transplantation
- No new drugs approved in AML since 1990...UNTIL 2017!

Burnett AK, Hematology Am Soc Hematol Educ Program 2012

Management of AML in 2018

- Divided into therapy for younger (<60-65 years) versus older pts (>65 yrs)
- Induction chemotherapy: Goal = CR (<5% blasts)
  - “Standard” induction = “7+3”
    - 7 days of continuous infusion cytarabine
    - 3 days of anthracycline (daunorubicin v. idarubicin)
  - Induction therapy advanced with new drug approvals for specific subsets of AML pts
    - Midostaurin - FLT3 inhibitor; front-line treatment with 7+3 for newly dx AML with FLT3 mutations
    - CPX-351 - Liposomal Cytarabine and Daunorubicin approved for t-AML and AML with MDS-related changes or preexisting MDS
    - Gemtuzumab - Anti-CD33 antibody with calicheamicin toxin- approved in combination with 7+3
    - Enasidenib - IDH2 inhibitor, single-agent for relapsed/refractory AML

FLT3 as a Target

- FLT3 = fms-like tyrosine kinase-3
  - FLT3 = tyrosine kinase receptor -> cell survival, signaling, and proliferation
- FLT3 mutations seen in 25-30%
  - ITD mutation - most common - 3 to >200 base pairs inserted into FLT3 gene -> constitutive activation of FLT3
  - Younger pts, highly proliferative, most commonly normal cytogenetics, high rate of relapse
- TKD mutations - less common, neutral prognosis
- Thought to be a secondary “driver” of AML and co-occurs with other mutations

Clonality of AML

- AML is polyclonal at Dx
- After chemo and/or relapse-- becomes oligoclonal based on dominant clone

Ding et al. Nature 2012

7+3 + Midostaurin

- RATIFY Trial- RP3 trial of 7+3 + Midostaurin 50 mg PO Bid on days 8-21 vs. Placebo in <50 years with FLT3 mut.
- If CR-> Midostaurin added to consolidation and maintenance
- N=717 pts- CR rates = 59% vs. 54% (p=0.15)


- Midostaurin FDA-Approved in combo with 7+3 for newly Dx AML with FLT3 mutation- April, 2017
- First targeted agent approved for AML

CPX-351

- Liposomal formulation of 7+3
- RP2 study in newly Dx AML≥60 yrs vs. 7+3
  - CR rates = 67% vs. 51%, p=0.07
  - Median OS = 14.7 months vs. 12.9 months, lower 60-day mortality with CPX-351
- Secondary AML appeared to have most benefit
- RP3 study of CPX-351 vs. 7+3 in newly Dx secondary AML 60-75 years
  - N = 309 pts randomized
  - CR rates = 47.7% vs. 33.3% (p=0.016), Median OS = 9.6 months vs. 5.9 months (p=0.005)
- CPX-351 approved for first-line Tx of AML with MDS-related changes and t-AML (August, 2017)
- New SOC for an extremely high-risk AML patient population

Lense L. ASCO Abstract 2016
AML with MDS-Related Changes

<table>
<thead>
<tr>
<th>Complex karyotype (≥ 3 in more abnormalities)</th>
</tr>
</thead>
<tbody>
<tr>
<td>- i(17q)/t(15;17)</td>
</tr>
<tr>
<td>- t(8;21)</td>
</tr>
<tr>
<td>- del(5q)</td>
</tr>
<tr>
<td>- del(7q)</td>
</tr>
<tr>
<td>- del(12p)</td>
</tr>
<tr>
<td>- del(13q)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Balanced abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>- t(9:11)q(t:q31:32)</td>
</tr>
<tr>
<td>- t(15;17)</td>
</tr>
<tr>
<td>- t(14;18)</td>
</tr>
<tr>
<td>- t(11;13)</td>
</tr>
<tr>
<td>- t(9;22)</td>
</tr>
<tr>
<td>- t(8:21)</td>
</tr>
<tr>
<td>- t(10;11)</td>
</tr>
</tbody>
</table>

Arber D, Blood 2016

Gemtuzumab (GO)

- Initially FDA-approved in 2000 for relapsed/refractory AML
- Taken off market in 2010 due to toxicity & efficacy concerns in 2010
- ALFA-0701- RP3 study of 7+3 + GO vs. 7+3 in newly dx AML 50-70 yrs
  - GO incorporated into consolidation therapy
  - CR rates = 81% vs. 75% with GO (p=0.25), OS and EFS advantage with GO

Castaigne, Lancet 2012

GO- Back to the Future

- Re-approved in 2017- in combination with 7+3
- Favorable/Intermediate-risk cytogenetics benefit from GO
- Adverse-risk pts do not benefit
- SOC for Favorable/Intermediate-risk AML
- Consolidation studied only included 2 cycles- is this superior to 4 cycles of HiDAC?
- Unclear benefit over 7+3 with high dose daunorubicin
  - Daunorubicin 60 mg/m² studied with GO
How to Manage AML in Younger Pts in 2018

- Clinical trials are still imperative for newly dx AML
- Treatment individualized based on prognostic factors at Dx
  - If FLT3 mutation (typically back in 2-4 days) > 7+3 + Midostaurin
  - If favorable/intermediate-risk cytogenetics w/o FLT3 mutation and 50-70 years > 7+3 + GO
    - If <50 years > 7+3 with high dose daunorubicin versus 7+3 + GO
  - If t-AML, AML with MRC or preexisting MDS > CPX-351
  - Adverse-risk AML - no SOC, clinical trials versus 7+3 versus cladribine + 7+3
- Suspect treatment algorithms will continue to evolve as more targeted and selective agents are utilized

Alvocidib

- Novel agent in development for AML
- Potent CDK9 inhibitor
- Studied in >400 AML pts - newly dx & relapsed/refractory

> CR rates significantly higher with FLAM vs. 1 or 2 cycles of 7+3 (70% vs. 46% vs. 57%, respectively)
- OS no different between either arms
- Predictive biomarkers of response with Alvocidib?

Predictive Biomarkers of Alvocidib

- Alvocidib inhibits MCL-1
  - MCL-1 - anti-apoptotic peptide regulated by CDK9 and RNA polymer II
  - Retrospective BH3 profiling from diagnostic bone marrow samples from FLAM vs. 7+3
    - High NOXA priming score associated with MCL-1 dependence

Zeidner JF et al. Hematology 2015
Elderly AML

- Age >60-65 years
- Dismal prognosis - 5-year survival <10%
  - Increased toxicity and mortality with intensive induction
  - Higher rates of adverse-risk features
  - More aggressive disease biology independent of risk status
- Have not made significant therapeutic advances

Management of Elderly AML

- Optimal management is key area of research
- No “standard of care”
- 1) Decide if patient is fit or unfit for intensive chemo
  - Variety of objective comorbidity scores can be used
  - Many times = subjective assessment
- 2) Obtain diagnostic/prognostic information
  - Adverse-risk dz do poorly with intensive chemo
- 3) Clinical trials imperative for elderly AML

Elderly AML- Fit Patients

- Intensive chemo can be given to select FIT pts up to 75-80 yrs
  - Favorable-risk respond best
- CPX-351- SOC for newly diagnosed secondary AML
  - Pts should be fit to receive intensive chemo- RP3 trial- pts 60-75 yrs
  - Cytopenias tend to be longer with CPX-351
- 7+3- reasonable option for favorable-risk elderly AML
  - Should not use high dose daunorubicin
  - If ≤70 years and not adverse-risk > add GO to induction
  - Clofarabine- inferior to 7+3 for elderly AML (RP3 trial)
- Hypomethylating agents- Azacitidine or Decitabine
  - Lower intensity, no need for hospitalization, less toxicity
  - Lower rates of CR but unclear if difference in overall outcomes?
- Gemtuzumab- single agent
- Low dose cytarabine
RP3 Study of Azacitidine vs. Physician Choice in AML

- Newly Dx AML >65 years with ≤30% bone marrow blasts
- When compared with pts preselected for intensive chemo (7+3):
  - N= 87 randomized
  - Median OS = 13.3 months vs. 12.2 months with Aza vs. 7+3
  - CR rates = 28% vs. 47.7% with Aza vs. 7+3
- Reasonable first-line option in AML- trials in combination

Decitabine

- RP3 Study of Decitabine (5 day) vs. Physician choice (BSC or LDAC) in newly dx AML >65 years
  - Median OS = 7.7 months vs. 5.0 months; p=0.108
  - Not FDA-approved
  - CR rate = 18%
  - Decitabine 10-day regimen: CR rates as high as 50%
  - No randomized trials
  - Potential activity in TP53 mut

Clinical Trials in Elderly AML

- Venetoclax- BCL-2 inhibitor- RP3 trials ongoing in combination with 1) LDAC, 2) Azacitidine
- Pevonedistat- NEDD-8-Activating Enzyme Inhibitor- RP3 trial ongoing in combination with Azacitidine
- Phase 2 study of Azacitidine + Pembrolizumab
  - Multi-institutional trial- Hopkins, UNC, MUSC
  - 2 cohorts- A) Newly Dx AML >65 years, B) Relapsed/refractory
  - Enrolling at UNC- correlative studies to determine predictors of response
- Azacitidine + novel agent strategy
**Relapsed/Refractory AML**
- Majority of pts who achieve CR-> relapse
- No SOC, outcomes are extremely poor
- Treatment includes intensive salvage chemotherapy versus lower intensity treatments
- Phase 2 Study of High Dose Cytarabine + Pembrolizumab
  - Multi-institutional trial - UNC = Lead site
- Enrolled 22 pts to date - overall CR rates = 35%
- Correlative studies - predictive biomarkers of response

**Targeted Therapy**
- IDH2 mutations seen in 8-10% of AML
  - IDH2**R140** and IDH2**R172** mutations
  - Commonly associated with other mutations
- Enasidenib - First-in-class IDH2 inhibitor - oral agent
- Phase I/II study of Enasidenib in relapsed/refractory AML with IDH2 mutations
  - N=239 pts
  - Safe and effective dose = 100 mg daily
  - Overall response rate = 39%, CR rates = ~20%
  - Median duration of response = 5.6 months
- Enasidenib well tolerated - differentiation syndrome can occur in 12% of pts - need to be rigorously monitored
- FDA-approved for Tx of relapsed/refractory AML with IDH2 mutation in August, 2017

**Where Do We Go From Here?**
- Multitude of new agents being explored in AML
- Beginning to understand how best to Tx small subsets of pts
- Predictive biomarker strategies promising - moving away from 1-size fits all Tx
- Immunotherapeutic strategies represent promising avenue of exploration in AML
Case

- 67 yo M with past medical history significant for Stage I Squamous Cell Carcinoma of Oropharynx in 2015, s/p Cisplatin + XRT, with no evidence of recurrence, presents with progressive fatigue, chest tightness and found to have pancytopenia with WBC = 1.3x10^9/L, Hb = 7.8 g/dL, and platelet count = 69x10^9/L. A bone marrow biopsy is performed revealing 20% blasts by manual aspirate differential with multilineage dysplasia. Cytogenetics reveal a highly complex karyotype and NGS mutational testing reveals TP53 mutation. The patient otherwise has an ECOG PS = 0 and is healthy with minimal other comorbidities.

Question 1

What is the next step in the management of this patient?
A) Refer directly for allogeneic stem cell transplant
B) 7+3 induction chemotherapy
C) CPX-351
D) Azacitidine
E) 7+3 + Midostaurin
Conclusions

- AML is a challenging Dz to treat
  - Heterogeneous with diverse genetic subsets
- AML pts have a poor prognosis
- 4 new agents approved in AML in 2017
  - Significantly improving outcomes for subsets of pts
  - Standard Rx’s are still unsatisfactory
- Prompt referral to highly specialized cancer centers is warranted
- Clinical trials are imperative in all facets of Dz

Questions?

E-Mail: Joshua_Zeidner@med.unc.edu
Office: 919-962-5164