AML: Are We Finally Making Real Progress?

Jessica K. Altman, MD

Robert H. Lurie Comprehensive Cancer Center of Northwestern University
Audience Polling Results

Are We Making Progress?
1. YES!!!
2. Nope, not at all - just an excuse for Altman to come to Manhattan
3. Maybe some incremental improvement for some subtypes of AML

39%

4%

56%
Learning Objectives

• Identify the targeted therapies emerging for the treatment of AML
• Be aware of how the efficacy of these agents may (or may not) be dependent on specific mutations
AML Introduction

• Estimated new cases/deaths (US) 2016: 19,950/10,430
  • ~25% will survive 5 years
• Median age: 67 years
• Heterogeneity in genetics, clinical manifestations, and outcome
• New targeted agents promising
• We will only make real progress when we can better name and define “AML”

Stop Apologizing...AML is not AML

- 25 yo: pancytopenia (or higher WBC ct), large ecchymosis, and DIC
- t(15;17)
- FLT3 ITD +

- 25 yo: high white blood cell ct, gingival hyperplasia, tumor lysis syndrome
- NK
- FLT3 ITD +

Progress occurring thru understanding biology
Approach to Newly Diagnosed Patient

- History and physical (organomegaly, EMD)
- CBC with differential, chemistry panel including uric acid
- Smear review
- PT, PTT, fibrinogen (DIC panel)
- Bone marrow aspirate and biopsy
  - Morphology
  - Flow cytometry
  - Cytogenetics — prognosis, treatment, role of transplant
  - Molecular studies — prognosis, role of transplant, targeted treatment (had been restricted to trials but not for long)
- Hydration, allopurinol or rasburicase, transfusions as needed
- Risk assessment and HLA typing
- Discussion of fertility
Overall Survival
Adults < 60 years
## Evolution of Prognostic Factors in AML

<table>
<thead>
<tr>
<th>Time Period</th>
<th>Prognostic Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior to 1980s</td>
<td>Age, WBC, antecedent hematologic disorder</td>
</tr>
<tr>
<td>1980s – 1990s</td>
<td>Cytogenetics</td>
</tr>
<tr>
<td>1990s – 2000s</td>
<td>Molecular genetics (<em>FLT3, MLL, NPM1, CEBPa, c-KIT, IDH, TET2, RUNX1, p53</em> and growing) and interactions</td>
</tr>
</tbody>
</table>
## Acute Myeloid Leukemia

### RISK STATUS BASED ON VALIDATED CYTOGENETICS AND MOLECULAR ABNORMALITIES

<table>
<thead>
<tr>
<th>RISK STATUS</th>
<th>CYTOGENETICS</th>
<th>MOLECULAR ABNORMALITIES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favorable-risk</td>
<td>Core binding factor: inv(16) or t(16;16) or t(8;21) or t(15;17)</td>
<td>Normal cytogenetics: NPM1 mutation in the absence of FLT3-ITD or isolated biallelic CEBPA mutation</td>
</tr>
<tr>
<td>Intermediate-risk</td>
<td>Normal cytogenetics: +8 alone or t(9;11) or Other non-defined</td>
<td></td>
</tr>
<tr>
<td>Poor-risk</td>
<td>Complex (≥3 clonal chromosomal abnormalities): Monosomal karyotype: -5, 5q+, -7, 7q-, 11q23 - non t(9;11); inv(3), t(3;3), t(6;9), t(9;22)</td>
<td>Normal cytogenetics: with FLT3-ITD mutation or TP53 mutation</td>
</tr>
</tbody>
</table>

AML-A

© 2016 National Comprehensive Cancer Network. All rights reserved. These guidelines and this illustration may not be reproduced in any form without the express written permission of NCCN®. To view the most recent and complete version of the NCCN Guidelines, go online to NCCN.org.
What Has Resulted in Improvement?

• Biology
• Naming – better prognostic assessment
• Continued improvement in transplant – understanding which disease characteristics warrant transplant in CR1, having greater donor availability, and refining transplant modalities
• Updating standard treatments and incorporating novel agents
Acute Myeloid Leukemia – Approach to Targeted Therapies

• AML defined by cytogenetic and molecular interactions
• Prognosis determined by cytogenetic and molecular abnormalities
• Incorporation of novel agents in relapsed/refractory AML
• Use of novel agents in newly diagnosed patients
Therapies Thought Not to Depend on Mutational Complexity

- Anthracycline intensification
- Different formulations of 7+3: CPX-351 (vosaroxin)
- Anti CD33 Abs
- BCL-2 inhibition
Randomized Trials of Escalated Daunorubicin (90 vs 45 mg/m2)

- **ECOG trial:** CR and OS benefit intermediate risk improvement in OS in FLT3 ITD+ pts
- **HOVON trial:** CR and OS benefit in 60-65 years and core-binding factor
- **KSH Trial:** CR and OS benefit in intermediate risk
- **UK NCRI trial:** No benefit of 90 over 60 (but everyone got 2nd cycle induction)

CPX-351

• CPX-351 - liposomal formulation of cytarabine and daunorubicin
  • 5:1 molar ratio
  • In vitro: highest level of synergy and the lowest level of antagonism
• Randomized phase III: CPX-351 vs 7+3 in adults w secondary AML
  • 60-75 yo w prior cytotoxic treatment, antecedent MDS or CMML, or AML with MDS-related cytogenetic abnormalities
• CPX-351 median OS 9.56 vs. 5.95 mo for 7+3 (HR=0.69; P=0.005)
• Improved EFS (HR=0.74; P=0.021)
• CR+CRi response 47.7% vs. 33.3%; (P=0.016)
• Grade 3-5 AEs were equal (92% vs. 91%) and were similar in frequency and severity in both arms. Similar numbers of patients were transplanted in both arms

Lancet J, ASCO 2016
CD33 as a target

- SGN-CD33A: stable dipeptide linkers that enable uniform drug loading of a pyrrolobenzodiazepine dimer that crosslinks DNA leading to cell death
- Phase I: CR+CRi 41% (40 mcg/kg); 58% in 12 treatment-naïve
- Combined w hypomethylating agents (HMA)
  - CR + CRi + CRp of 58%; median relapse free survival of 7.7 mo
- Phase III randomized trial planned

Stein et al.; ASH abstr #324, 2015
Fathi et al. ASH abstr #454, 2015
BCL-2

• ABT-199/venetoclax is a small-molecule BCL2 inhibitor leading to the initiation of apoptosis

• Phase Ib trial in combo w HMA - overall CR rate of 35% and CRi rate of 35%, CR+ CRi rate of 71%

• Phase Ib/2 in combo w low-dose cytarabine:
  • CR +CRi rate of 54%
  • Responses even if prior HMA exposure
  • 1 yr OS of 70.5% in non MPN pts and 57.6% in MPN pts

Dinardo et al. ASH abstr #327, 2015
Lin et al. ASCO abst #7007, 2016
### Mutations of Importance in Practice Today

<table>
<thead>
<tr>
<th>Gene</th>
<th>Incidence</th>
<th>Associations</th>
<th>Impact</th>
</tr>
</thead>
<tbody>
<tr>
<td>FLT3-ITD</td>
<td>30%</td>
<td>NPM1</td>
<td>Unfavorable</td>
</tr>
<tr>
<td>NPM1</td>
<td>30%</td>
<td>FLT3</td>
<td>Favorable</td>
</tr>
<tr>
<td>CEBPa</td>
<td>9%</td>
<td>FLT3</td>
<td>Favorable</td>
</tr>
<tr>
<td>C-KIT</td>
<td>6%1</td>
<td>CBF</td>
<td>Unfavorable [in t(8;21), but less clear in inv(16)/t(16;16)]</td>
</tr>
</tbody>
</table>

Novel Agents – Mutation Specific

- FLT3
- IDH
Case

• Deb, 52-year-old female, presented to her PCP with a week of fever of 103 F, generally feeling unwell.

• Because of the persistent symptoms, a CBC is drawn revealing WBC of 196,000/uL, Hgb of 5.7 g/dL, and PLT count of 80,000/uL.

• She is instructed to go to the Emergency Room for urgent evaluation. At the ER, her exam is notable only for scattered bruises and mild gingival hyperplasia.

• She undergoes bone marrow evaluation and is diagnosed w AML with NK and a FLT3 ITD
FLT3 as an AML Target

- Promotes proliferation and blocks differentiation
- Over-expressed in the majority of AML cases
- Activating mutations present in 25%–40% of AML (ITD and activation loop)
- Patients with FLT3/ITD mutations have a worse prognosis – increased relapsed rate, lower OS
- Associated with leukocytosis and high percentage of bone marrow blasts, de-novo AML
- FLT3 inhibitors in development; single agent and combination studies

Treatment

• Enrolled on C10603: A Phase III Randomized, Double-Blind Study of Induction (Daunorubicin/Cytarabine) and Consolidation (High-Dose Cytarabine) Chemotherapy + Midostaurin (PKC412) or Placebo in Newly Diagnosed Patients < 60 Years of Age with FLT3 Mutated AML

• Attained aplastic marrow at day 14 and then entered CR ~ day 28

• Matched sibling donor allogeneic stem cell transplant in CR1
C10603 Schema

PRE-REGISTER

Stratify* FLT3 ITD or TKD

FLT3 WILD TYPE not eligible for enrollment

RANDOMIZE

Daunorubicin ARA-C

HiDAC Midostaurin

Midostaurin MAINTENANCE 12 months

CR

X 4

Daunorubicin ARA-C

HiDAC Placebo

Placebo MAINTENANCE 12 months

CR

X 4

Stratification: TKD; ITD with allelic ratio <0.7 vs. ≥0.7

Stone et al. ASH, abst #6, 2015
Midostaurin Results

- CR rate by day 60 in midostaurin arm 59% vs 53% in placebo arm (NS)
- CR w induction and consolidation: 66% vs 59% (p = 0.045)
- Median OS: Midostaurin 74.7 (31.7-NE); placebo 25.6 (18.6-42.9) mo (HR 0.77; 1 sided p 0.0074)
- Midostaurin improves OS when added to standard chemo with maintenance in newly diagnosed patients aged 18-60 with ITD and TKD FLT3 mutant AML and represents a new standard of care

Stone et al. ASH, abst #6, 2015
Back to our case

• Deb has no major transplant related complications
• Disease recurrence at ~ day 130 as her immune suppression was being weaned
What would you offer her at this time?

1. Hospice - she had an early relapse
2. Immune withdrawal alone
3. Re-induction chemotherapy
4. 5-aza + sorafenib
5. Clinical trial

1%  7%  24%  16%  51%
What happened to Deb?

• Treated with sorafenib + 5-aza and disease entered remission, underwent DLI and then maintenance sorafenib (has been 3 years since disease recurrence)

• 43 adults w relapsed/refractory AML treated with 5-aza + sorafenib:
  • RR of 46%, with 27% CRi, 16% CR, and 3% PR
  • Median time to achieve CR/CRi was 2 cycles
  • Median duration of CR/CRi was 2.3 months (range, 1-14.3 months)

Ravandi F. Blood 2013
Survival Among FLT3-ITD AML Patients Following HCT in CR1

2-year OS and DFS were better among patients treated with sorafenib (83% and 85%, respectively) compared to controls (58%, p=0.0047 and 52%, p=0.0065)

2-year Cumulative incidence of AML relapse was 9.5% for sorafenib patients and 41% for controls, p=0.0065; 2-year non-relapse mortality was 5.7% and 7.6%, respectively, p=0.61

Brunner AM et al. ASH 2015, abstract 864
## Gilteritinib for Relapsed/Refractory FLT3 ITD AML

<table>
<thead>
<tr>
<th>Clinical Response</th>
<th>≥80 mg Gilteritinib</th>
<th>TKI Status</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mutation Type</td>
<td>TKI Status</td>
</tr>
<tr>
<td></td>
<td>FLT3-ITD only</td>
<td>Prior TKI</td>
</tr>
<tr>
<td></td>
<td>FLT3-D835 only</td>
<td>TKI Naïve</td>
</tr>
<tr>
<td></td>
<td>ITD and D835</td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>N=142</td>
<td>N=40</td>
</tr>
<tr>
<td></td>
<td>16 (11)</td>
<td>2 (5)</td>
</tr>
<tr>
<td>CRp</td>
<td>11 (8)</td>
<td>3 (8)</td>
</tr>
<tr>
<td>CRi</td>
<td>38 (27)</td>
<td>9 (23)</td>
</tr>
<tr>
<td>PR</td>
<td>15 (11)</td>
<td>5 (13)</td>
</tr>
<tr>
<td>CRc (CR+CRp+CRi)</td>
<td>65 (46)</td>
<td>14 (35)</td>
</tr>
<tr>
<td>ORR (CRc+PR)</td>
<td>80 (56)</td>
<td>57 (45)</td>
</tr>
</tbody>
</table>

Data presented as n (%).

CR, complete remission; CRc, composite complete remission; CRp, complete remission with incomplete platelet recovery; CRi, complete remission with incomplete hematologic recovery; ORR, overall response rate; PR, partial response.

Across all FLT3+ subjects treated with gilteritinib ≥80 mg:
Median duration of response was 111 (range: 8–383) days
Median overall survival was 218 (range: 12–430) days
Randomized trial in R/R AML ongoing

Altman et al. ASH abstr #321, 2015
Setting of FLT3 Inhibitor Studies

Figure 1. Settings for the incorporation of novel targeted therapies. MRD: minimal residual disease. *FLT3 Inhibitors have been investigated in these contexts. ¹For patients in complete remission. ²For patients with relapsed or refractory disease.

Grunwald MR and Levis MJ, Seminars in Hematology, 20
# Mutations of Increasing Importance

<table>
<thead>
<tr>
<th>Gene</th>
<th>Incidence</th>
<th>Associations</th>
<th>Impact</th>
</tr>
</thead>
<tbody>
<tr>
<td>IDH1/2</td>
<td>7%/8%</td>
<td>NPM1+/FLT3-</td>
<td>Favorable</td>
</tr>
<tr>
<td>DNMT3A</td>
<td>22%</td>
<td>Intermed-risk cyto.</td>
<td>Unfavorable</td>
</tr>
<tr>
<td>TET2</td>
<td>8%</td>
<td>NPM1</td>
<td>Unfavorable</td>
</tr>
<tr>
<td>ASXL1</td>
<td>3%</td>
<td>Intermed-risk cyto.</td>
<td>Unfavorable</td>
</tr>
</tbody>
</table>
IDH Mutations Associated With Oncogenic Changes

- IDHwt: catalyzes oxidative decarboxylation of isocitrate to produce CO₂ and α-KG

- 3 isoforms exist: IDH1, IDH2, IDH3
  - IDH1: cytoplasm
  - IDH2: mitochondria

- IDH mutations have neomorphic activity:
  - Produce “oncometabolite” 2-HG (gain of function)
  - Lead to oncogenic alterations in cellular metabolism

Practice Changing Treatments in AML

Allogeneic Transplant

1970

7+3

1980

Daunorubicin Intensification

1990

Cytarabine Consol

2000

FLT3 Inhibitors

2010

Thomas et al. NEJM, 1979; Mayer et al. NEJM, 1994; Fernandez et al. NEJM, 2009, Stone et al. ASH abst #6, 2015
Acknowledgements:
Leukemia Program of Northwestern University
Northwestern Medicine Developmental Therapeutics Program
ECOG-ACRIN

j-altman@northwestern.edu