Finally!….. Progress in AML

Eunice S. Wang MD
Leukemia Service
Roswell Park Cancer Institute
AML is most frequently diagnosed between ages 65-74

"Young" < 60 years old

"Old" ≥ 60 years old

Standard 7+3 induction therapy

7 days + 3 days
Cytarabine + Daunorubicin
60-90 mg/m²

OR

Idarubicin
12 mg/m²
High dose induction chemotherapy has been the standard since the 1980s.

“This will buy you four months.”
Chemotherapy better than no chemo in decreasing early death rates in AML

Swedish Registry Data (Juliusson G et al. Blood 2009;113:4179-4187)
Outcomes of 7+3 depend on age

(Swedish registry data 2000-2006, N=3205)

Juliusson et al. Clinical Lymphoma Myeloma and Leukemia 11; Supplement 1 2011 S54 – S59

Appelbaum et al. Blood 2006;107: 3481-3486
Comorbidity in older adults is common and linked with treatment-related toxicity

Comorbidity is common among older adults receiving induction therapy

- Prospective study (N=177)
- Aged ≥ 60 years
- Received induction chemotherapy
- Used HCT-CI

Increased comorbidity burden associated with increased toxicity

76% pts have 1-2

Giles et al. Br J Haematology 2007
Hypomethylating agents (HMA)

- **Azacitidine (Vidaza)** 75 mg/m² sq/IV qd for 7 days
- **Decitabine (Dacogen)** 20 mg/m² IV qd for 5-10 days

- Multiple courses of therapy required for efficacy
- Treatment indefinite to maintain response/ stable disease
- Side effects: Low counts with risk of infection, nausea, constipation, fever and injection site reactions (sq)
Survival with azacitidine equivalent to conventional chemotherapy in older AML pts

AML is characterized by mutational complexity

Papaemmanuil E et al NEJM 374(23): 2209-221, 2016
INTEGRATION OF IMPROVED MOLECULAR PROFILING IN THE DIAGNOSTIC ALGORITHM OF AML

Morphology  

FISH  

Cytogenetics  

Flow cytometry

Next-generation sequencing-based mutation profiling

- FLT3
- DNMT3A
- TET2
- MLL-PTD
- WT1
- NPM1
- CEBPA
- IDH1/2
- ASXL1
- RUNX1
- TP53

Risk stratification  

Mutation-based drug discovery  

MRD monitoring
What comprehensive mutational profiling tells us about AML

• Where AML came from
  – Insight into underlying disease biology

• Whether AML will respond to standard therapy
  – Predicts outcome to 7+3 chemotherapy

• Whether targeted therapies are an option
  – Upfront
  – Relapsed/refractory setting
  – Minimal residual disease
Outcome of 7+3 depends on cytogenetics and mutational profile

- 1540 pts treated with 7+3 on 3 prospective trials

Papaemmanuil E et al NEJM 374(23): 2209-221, 2016
Treatment Algorithm

Newly diagnosed adult patient with AML

- If WBC >100K or Organ failure
  - Inpatient emergent leukopheresis, hydroxyurea, chemo

Fitness for therapy (fit, unfit, frail)
- Cytogenetic and mutational profiling

Appropriate for therapy

- Inpatient emergent leukopheresis, hydroxyurea, chemo
- Favorable risk AML
  - Intensive chemo or clinical trial
- Intermediate risk AML
  - Intensive chemo or HMA or clinical trial
- Targetable mutation (i.e. FLT3)
  - Clinical trial of Intensive chemo or HMA + inhibitor
- Adverse risk AML
  - HMA or clinical trial

Chemotherapy or bone marrow transplant
Case 1: Ms. N.F.

- **73 year old** woman with prior history of NHL (dx 2012 Rx with CHOP x 6 cycles and localized radiation therapy
- Presents with progressive cytopenias
- Labs: WBC 5.44, differential shows 36% blasts, Hgb 7.9 gm/dl, Plts 137K
- Marrow morphology: 81% myeloid blasts -> AML
- Cytogenetics: 46 XX normal karyotype

**Mutational profile:**

- ABL1 (NUP214-ABL1 fusion),
- MLL exon 3-7, RUNX1, SRSF2
Presence of certain mutations are highly (>95%) specific for secondary AML

Mutation-defined secondary AML pts have worse outcomes to 7+3 than de novo AML

Secondary AML

- **Mutations:** *NUP214-ABL1, MLL exon 3-7, RUNX1, SRSF2*

- **Diagnosis:** Clinical/mutation evidence of secondary AML

- **Prognosis:** Likely poor outcome to standard 7+3

- **Therapy:**
  - CPX-351 (Vyxeos = liposomal 7+3) awaiting FDA approval
  - ABL inhibitor (dasatinib), spliceosome inhibitor
  - SGN-33A (Vadastuximab talirine) + HMA trial => achieved CR and received 4 mos of Rx before succumbing to sepsis
CPX-351 (Vyxeos)

- **Vyxeos** is a liposomal formulation of cytarabine and daunorubicin encapsulated at a 5:1 molar ratio
  - This ratio maximizes synergy and minimizes antagonism *in vitro*¹

- Fixed molar ratio maintained for at least 24 hours after final dose²
  - Drug exposure was maintained for 7 days

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CPX-351 Phase III Study Design

- Randomized, open-label, parallel-arm, standard therapy–controlled
  - 1:1 randomization, enrolled from December 2012 to November 2014
  - Patients with complete response (CR) or CR with incomplete platelet or neutrophil recovery (CRi) were to be considered for allogeneic HCT, based on institutional criteria

Key Eligibility
- Previously untreated
- Ages 60–75
- Able to tolerate intensive therapy
- ECOG PS 0–2

Stratifications:
- Therapy-related AML
- AML with history of MDS with and without prior HMA therapy
- AML with history of CMML
- De novo AML with MDS karyotype
  - 60–69 years
  - 70–75 years

CPX-351 (n=153)

Daunorubicin 60mg/m²

Induction (1–2 cycles)

CPX-351 (n=73)

Follow-up:
- Death OR
- 5 years

Patients in CR/CRi: Consolidation (1–2 cycles)

7+3 (n=52)

7+3 (n=156)

AML, acute myeloid leukemia; CMML, chronic myelomonocytic leukemia; CR, complete response; CRi, CR with incomplete platelet/neutrophil recovery; ECOG PS, Eastern Cooperative Oncology Group performance status; HMA, hypomethylating agents; MDS, myelodysplastic syndrome.

CPX-351 improves survival in secondary AML

Kaplan-Meier Curve for Overall Survival
ITT Analysis Population

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Events/N</th>
<th>Median Survival (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPX-351</td>
<td>104/153</td>
<td>9.56 (6.60, 11.86)</td>
</tr>
<tr>
<td>7+3</td>
<td>132/156</td>
<td>5.95 (4.99, 7.75)</td>
</tr>
</tbody>
</table>

Hazard ratio = 0.69
P value = 0.005

_J Lancet et al. ASCO 2016_
CPX-351 improves Survival from Transplant

• CPX-351 median OS not reached vs 10.25 months for 7+3
  – HR of 0.46 favoring CPX-351 ($P=0.0046$)
  – Cox proportional hazards HR, including transplant as a time-dependent covariate, was 0.51 (95% CI, 0.35–0.75; $P=0.0007$), favoring CPX-351

91 pts had alloSCT
- 52 (34%) CPX-351
- 39 (25%) 7+3

*J* Lancet *et al*  
ASH 2016  
*Oral presentation*
CPX-351 associated with lower overall mortality by Day 100 after transplant

- Day 100 mortality was lower in the CPX-351 arm
  - Lower mortality in patients with refractory AML in the CPX-351 arm

<table>
<thead>
<tr>
<th>Causes of Death &lt;100 Days</th>
<th>CPX-351 n=52 n (%)</th>
<th>7+3 n=39 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any cause</td>
<td>5 (9.6)</td>
<td>8 (20.5)</td>
</tr>
<tr>
<td>Refractory AML</td>
<td>2 (3.8)</td>
<td>3 (7.7)</td>
</tr>
<tr>
<td>Graft-vs-host disease</td>
<td>2 (3.8)</td>
<td>1 (2.6)</td>
</tr>
<tr>
<td>Renal</td>
<td>0</td>
<td>1 (2.6)</td>
</tr>
<tr>
<td>Respiratory</td>
<td>0</td>
<td>1 (2.6)</td>
</tr>
<tr>
<td>Multi-organ failure</td>
<td>0</td>
<td>1 (2.6)</td>
</tr>
<tr>
<td>Septic shock</td>
<td>0</td>
<td>1 (2.6)</td>
</tr>
<tr>
<td>Unknown</td>
<td>1 (1.9)</td>
<td>0</td>
</tr>
</tbody>
</table>

J Lancet et al ASH 2016
Vadastuximab talirine (SGN-33A): Mechanism of action

- Anti-CD33 antibody, engineered cysteines to enable uniform site-specific conjugation
- Cleavable dipeptide linker, highly stable in circulation
- Pyrrolobenzodiazepine (PBD) dimer, binds DNA with high intrinsic affinity

- Binds to CD33 antigen
- Complex is internalized and traffics to lysosome
- Increased CD33 cell surface density
- Increased PBD dimer binding to DNA
- PBD dimer is released
- DNA repair failed
- PBD dimer crosslinks DNA
- Apoptotic cell death
HMA priming before 33A results in:

- Modest increase in CD33 density on the cell surface
- Increased incorporation of PBD dimer into DNA
- Enhanced cytotoxicity (Sutherland et al, 2015 Blood; 126 (3): 3785)
Vadastuximab Talirine Plus Hypomethylating Agents: Study Design

Key Eligibility Criteria

- CD33-positive AML
- Declined high-dose induction/consolidation therapies
- No prior hypomethylating agents

Fathi et al: Oral presentation ASH 2016
<table>
<thead>
<tr>
<th></th>
<th>All Patients (N=53)</th>
<th>Patients with Secondary AML (N=23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range)</td>
<td>75 (60, 87)</td>
<td>77 (60, 87)</td>
</tr>
<tr>
<td>≥75 years</td>
<td>55%</td>
<td>70%</td>
</tr>
<tr>
<td>Gender, male</td>
<td>64%</td>
<td>70%</td>
</tr>
<tr>
<td>ECOG status (0/1)</td>
<td>21/79%</td>
<td>22/78%</td>
</tr>
<tr>
<td>MRC cytogenetic risk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermediate</td>
<td>62%</td>
<td>30%</td>
</tr>
<tr>
<td>Adverse</td>
<td>38%</td>
<td>70%</td>
</tr>
<tr>
<td>Wheatley risk*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Good/Standard</td>
<td>13/28%</td>
<td>-</td>
</tr>
<tr>
<td>Poor</td>
<td>55%</td>
<td>96%</td>
</tr>
<tr>
<td>Underlying myelodysplasia</td>
<td>42%</td>
<td>57%</td>
</tr>
<tr>
<td>FLT3+</td>
<td>11%</td>
<td>13%</td>
</tr>
<tr>
<td>NPM+/FLT3-</td>
<td>8%</td>
<td>-</td>
</tr>
<tr>
<td>Enrollment % bone marrow blasts (range)</td>
<td>52.5 (20, 90)</td>
<td>46.8 (20, 90)</td>
</tr>
<tr>
<td>Baseline median WBC x10^3/uL (range)</td>
<td>2.1 (0.4, 132)</td>
<td>2.0 (0.8, 18.9)</td>
</tr>
</tbody>
</table>

*Data not available for 2 patients

*Fathi et al: Oral presentation ASH 2016*
## Clinical Response: Efficacy Evaluable Patients

<table>
<thead>
<tr>
<th>Efficacy Evaluable</th>
<th>All N=49</th>
<th>Secondary AML&lt;sup&gt;d&lt;/sup&gt; N=22</th>
<th>FLT3/ITD+ N=5</th>
<th>Age ≥75 years N=26</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remission Rate (CR + CR&lt;sub&gt;i&lt;/sub&gt;)</td>
<td>73%</td>
<td>77%</td>
<td>100%</td>
<td>65%</td>
</tr>
<tr>
<td>CR</td>
<td>47%</td>
<td>50%</td>
<td>80%</td>
<td>38%</td>
</tr>
<tr>
<td>CR&lt;sub&gt;i&lt;/sub&gt; (p)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>20%</td>
<td>18%</td>
<td>20%</td>
<td>19%</td>
</tr>
<tr>
<td>CR&lt;sub&gt;i&lt;/sub&gt; (n)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>6%</td>
<td>9%</td>
<td>0</td>
<td>8%</td>
</tr>
<tr>
<td>mLFS&lt;sup&gt;c&lt;/sup&gt;</td>
<td>2%</td>
<td>5%</td>
<td>0</td>
<td>4%</td>
</tr>
<tr>
<td>ORR (CR + CR&lt;sub&gt;i&lt;/sub&gt; + mLFS)</td>
<td>76%</td>
<td>82%</td>
<td>100%</td>
<td>69%</td>
</tr>
</tbody>
</table>

<sup>a</sup> CR<sub>i</sub> (p)= CR with ANC ≥1000/uL, incomplete platelet recovery

<sup>b</sup> CR<sub>i</sub> (n)= CR with platelets ≥100,000/uL, incomplete neutrophil recovery

<sup>c</sup> mLFS = morphologic leukemia-free state

<sup>d</sup> Defined as therapy-related AML, AML evolved from prior MDS, or de novo AML with MDS-related cytogenetics

+Fathi et al: Oral presentation ASH 2016
Overall Survival: All Treated Patients

- Median overall survival for all pts = 11.3 mos
- 28% of patients remain alive and on study with a median follow up of 14.7 mos
- Median survival for pts with secondary AML (n=24) = 9.7 mos
- Median survival for pts ≥75 yrs old (n=29) = 12.7 mos

Fathi et al: Oral presentation ASH 2016
Case 2: Mr. S.R.

- 24 year old man with no prior medical history
- Presents with 2 weeks of progressive fatigue, swollen lymph nodes, intermittent fevers and anorexia, ruled out for mono
- Labs: **WBC 248K**, Hgb 9.6, plts 71K, differential 93% immature blasts
- Marrow/flow: 90% myeloblasts -> AML
- Cytogenetics: 46 XY, normal

**Mutational profile:** *FLT3-ITD, NUP98, WT1*
Presence of *FLT3*-ITD mutation is associated with poor outcome to 7+3 chemotherapy

**FLT3 inhibitors in development for therapy of FLT3 mutant AML patients**

**Multi-kinase inhibitor**
- **FLT3 kinase**
- Other kinases
- PKC-412 (Midostaurin)

**Specific FLT3 inhibitor**
- Potent highly specific for FLT3
- AC220 (Quizartinib)
- ASP2215 (Giltartinib)
- Crenolanib

*Zarrinkar PP et al. Blood 2009;114:2984-2992*
Addition of Midostaurin to 7+3 improves survival in younger FLT3 mutant AML patients

Stone et al. Blood 2015;126:6 (ASH plenary session)
Pilot study of Crenolanib + 7+3 in newly diagnosed FLT3 mutant AML patients

- Highly selective FLT3 inhibitor
- Inhibits both ITD and TKD
- Lack of binding to C-KIT
- Short half-life (TID dosing)
- Steady state PK (no accumulation)

Wang et al., Proc. ASH: 2016. abstract 1071
Crenolanib plus 7+3 results in high responses in FLT3 mutant AML patients

Response rates
- 28 (88%) of 32 in CR
- 16 (42%) to alloSCT

84% of pts tolerated full dose crenolanib + 7+3

Wang E et al Oral presentation at ASH meeting, December 6, 2016, abstract 1071

RPCI was the top accruing site with 15 patients enrolled

>85% survival at 6 mos

Median follow-up: 6 months (range 0.6-16.6 months)

N=32 pts

Number at risk

0 20 40 60 80 100
ARO-006 OS
0 2 4 6 8 10 12 14 16 18
Months
Survival probability (%)
Number at risk
38 29 24 19 14 6 3 1 1 0
Median follow-up: 6 months 
(range 0.6-16.6 months)
De novo *FLT3* mutant AML

- **Mutational profile:*** FLT3-ITD, NUP98, WT1

- **Diagnosis:** De novo *FLT-3* mutant AML
- **Prognosis:** Short disease free survival with 7+3 only

- **Therapy:** Clinical trial of FLT3 inhibitor + 7+3 followed by SCT

- **Outcome:** Enrolled on *crenolanib* + 7+3 trial -> HIDAC consolidation x 2 -> MRD alloSCT-> remains in remission following transplant with no evidence of AML
Case 3: R. I

- 56 year old woman with AML (complex karyotype)
- Refractory to 7+3 (2 cycles), azacitidine (6 mos), decitabine
- Also failed clinical trial with mylotarg +/- azacitidine

- Labs: WBC 83.8K, Hgb 6.6, plt 6K, 92% peripheral blasts
- Cytogenetics: Complex

- Mutational profile: IDH2 R172, ASXL1, ETV6-CHIC2
IDH Mutations as a Target in AML

- **Isocitrate dehydrogenase (IDH)** is a critical enzyme of the citric acid cycle

- IDH mutations occur in a spectrum of solid and hematologic tumors\(^1\):
  - IDH2 mutations: 9–13% of AML and 3–6% of MDS
  - IDH1 mutations: 6–10% of AML and 3% of MDS

- IDH1/2 mutations confer a gain-of-function\(^2\):
  - increased histone and DNA methylation
  - impaired cellular differentiation

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\(^1\)Based on literature analysis. Estimates will\(^2\) Dang et al. *Nature* 2009;462:739-44.
AG-221 (enasidenib) induces differentiation effects in *IDH2* mutant AML

**SCREENING**
40% Blasts

**C1D15**
Evidence of Appropriate Differentiation of Cells

**C3D1**
4% Blasts

*Stein EM ASH oral presentation 2015*
AG-221 (enasidenib) induces responses and stable disease in *IDH2* mutant AML patients

### Response

<table>
<thead>
<tr>
<th></th>
<th>RR-AML (n = 159)</th>
<th>Untreated AML (n = 24)</th>
<th>MDS (n = 14)</th>
<th>All (N = 209)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall Response</strong></td>
<td>59 (37%) [30%, 45%]</td>
<td>10 (42%) [22%, 63%]</td>
<td>7 (50%) [23%, 77%]</td>
<td>79 (38%) [31%, 45%]</td>
</tr>
<tr>
<td><strong>CR</strong></td>
<td>29 (18%) [13%, 25%]</td>
<td>4 (17%) [5%, 37%]</td>
<td>3 (21%) [5%, 51%]</td>
<td>37 (18%) [13%, 24%]</td>
</tr>
<tr>
<td><strong>CRp</strong></td>
<td>1 (1%)</td>
<td>1 (4%)</td>
<td>1 (7%)</td>
<td>3 (1%)</td>
</tr>
<tr>
<td><strong>CRi</strong></td>
<td>3 (2%)</td>
<td>0</td>
<td>0</td>
<td>3 (1%)</td>
</tr>
<tr>
<td><strong>mCR</strong></td>
<td>9 (6%)</td>
<td>1 (4%)</td>
<td>3 (21%)</td>
<td>14 (7%)</td>
</tr>
<tr>
<td><strong>PR</strong></td>
<td>17 (11%)</td>
<td>4 (17%)</td>
<td>0</td>
<td>22 (11%)</td>
</tr>
<tr>
<td><strong>SD</strong></td>
<td><strong>72 (45%)</strong></td>
<td>9 (38%)</td>
<td>6 (43%)</td>
<td>96 (46%)</td>
</tr>
<tr>
<td><strong>PD</strong></td>
<td>16 (8%)</td>
<td>1 (4%)</td>
<td>0</td>
<td>11 (5%)</td>
</tr>
<tr>
<td><strong>Not evaluable</strong></td>
<td>18 (11%)</td>
<td>4 (17%)</td>
<td>1 (7%)</td>
<td>23 (11%)</td>
</tr>
</tbody>
</table>

*Stein EM ASH oral presentation 2015*
Primary refractory *IDH2* mutant AML

- **Mutational profile:** *IDH2 R172*, *ASXL1*, *ETV6-CHIC2*

- **Diagnosis:** Primary refractory AML with *IDH2* mutation

- **Therapy:** Compassionate exemption therapy with AG-221

- **Outcome:** Achieved complete remission without platelet recovery (WBC 7.7K, no blasts, hgb 14.5, plts 20K) for > 4 months
**Venetoclax: Specific bcl-2 inhibitor**

Binding of drug releases proapoptotic proteins and induces apoptosis in AML cells

Venetoclax therapy in older AML patients

Venetoclax + LDAC in older AML patients

Table 1. ORR and 12-month OS estimates

<table>
<thead>
<tr>
<th></th>
<th>All patients N=20</th>
<th>Prior HMA n=2</th>
<th>No prior HMA n=18</th>
<th>Prior MPN n=2</th>
<th>No prior MPN n=18</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (CR+CRi+PR), n (%)</td>
<td>15 (75)</td>
<td>2 (100)</td>
<td>13 (72)</td>
<td>0</td>
<td>15 (83)</td>
</tr>
<tr>
<td>12-month OS estimate, 95% CI</td>
<td>74.7% (49.4 – 88.6)</td>
<td>NA</td>
<td>71.8% (44.9 – 87.2)</td>
<td>NA</td>
<td>83.3% (56.8 – 94.3)</td>
</tr>
</tbody>
</table>

Venetoclax 600 mg was administered orally once daily on days 2 – 28 of Cycle 1 and days 1 - 28 of subsequent cycles. A 5-day dose ramp-up schedule was followed to reach the 600 mg dose. LDAC 20 mg/m² was administered s.c. daily on days 1-10 in 28-day cycles.

20 patients not considered eligible for intensive chemotherapy

A. Wei et al Oral abstract ASH 2016
Safety and efficacy of Venetoclax + LDAC

Figure 1. Overall survival in responders vs. non-responders

Responders (CR+CRi+PR, n=15) vs. Non-responders (n=5)

OS in responding AML pts not reached

A. Wei et al Oral abstract ASH 2016
Novel therapies based on actionable mutations

Morgan A S, and Yang D T Blood 2013;121:3546