Acute Myeloid Leukemia: Prognostication, Targeting and Sequencing Therapies

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Diagnosis: Multiple leukemic clones present

Clinical remission: loss of most leukemic clones

Relapse: Acquisition of new mutations in a pre-existing clone

Targeting Founder/Driver Mutations

Ding et al., Nature 2012

Trump cells

cell type:
- normal
- AML

mutations:
- founder (cluster 1)
- primary specific (cluster 2)
- relapse enriched (cluster 3)
- relapse specific (cluster 5)
- random mutations in HSCs
- pathogenic mutations

AML1 / UPN933124

Chemotherapy

Ding et al., Nature 2012
Mutational Complexity of Acute Myeloid Leukemia (AML)

AML: It’s (genomically) complicated!

The Cancer Genome Atlas Research Network
Acute Myelogenous Leukemia
(All Cases)
A BRIEF EXAMPLE OF THE IMPORTANCE OF REPEATING MOLECULAR TESTING FOR FLT-3 IN RELAPSED PATIENTS
AML
82 yo ♀

XX, NPM1

FLT3-ITD
Gilterinib

IDH2
Enasidinib

AZA-VEN

WBC
K/CUMM
WHAT MOST PROGNOSTIC CLASSIFICATIONS TELL US

I TOLD YOU I WAS SICK

Prognostic $\neq$ Predictive
Recently Approved Drugs for AML

- Gentuzumab ozogamicin (CBF AML – inv16, t(8;21))
- Vyxeos – 2\(^0\) AML, MDS associated
- Venetoclax + low dose cytarabine or azacytidine or decitabine (age > 75, comorbidities)
- Midostaurin (FLT3 – newly diagnosed)
- Gilteritinib (FLT3 - relapsed)
- 5-azacytidine ("unfit" for intensive therapy)
- Enasidenib (IDH2 mutated)
- Ivosidenib (IDH1 mutated)
- Glasdegib (hedgehog inhibitor)
Meaning that you have to have rapid access to molecular/cytogenetic results to rationally apply these “targeted” therapies...
FLT3 Inhibitors in AML

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)


Participants: ALLIANCE/CALGB, AMLSG, CETLAM, ECOG, EORTC, GIMEMA, NCIC, OSHO, PETHEMA, SAL, SWOG
CTEP sponsored, Novartis provided drug and sponsored outside North America, and Alliance (formerly CALGB) chaired study, collected data and performed analysis
Overall Survival (Primary Endpoint)

23% reduced risk of death in the Mido arm

- **Median OS**:
  - Mido: 74.7 (31.7-NE) months
  - PBO: 25.6 (18.6-42.9) months

- **Hazard Ratio**: 0.77
- **1-sided log-rank p-value**: 0.0074

- **Arm 4-year Survival**:
  - MIDO: 51.4% (95%CI: 46, 57)
  - PBO: 44.2% (95%CI: 39, 50)

* controlled for FLT3 subtype (TKD, ITD-Low, ITD-High)
PHARMA DESIGNED-DOMINATED
CLINICAL TRIALS

• Focused trials designed primarily for drug approval rather than addressing the questions which clinicians would consider to be clinically important

• Complicated and inefficient processes which affect the ability of U.S. cooperative groups to implement studies
The example of trials of FLT3 inhibition in AML
Simultaneous, separate trials are in progress in newly diagnosed patients using 7 & 3 (midostaurin) with or without quizartinib, crenolanib, gilteritinib, sorafenib, and others...

<table>
<thead>
<tr>
<th>FLT3 Inhibitors</th>
<th>Selectivity</th>
<th>Targets</th>
<th>Phases of Development</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sunitinib (SU11248)</td>
<td>Non-selective</td>
<td>c-KIT, KDR PDGFR, and FLT3</td>
<td>Phase II [26]</td>
<td>Decreased appetite, headache, GI symptoms</td>
</tr>
<tr>
<td>Lestaurtinib (CEP7011)</td>
<td>Selective</td>
<td>Mutated and wild-type FLt3</td>
<td>Phase II [28]</td>
<td>Infections, sepsis, central nervous system</td>
</tr>
<tr>
<td>Tandetanib (CT1069)</td>
<td>Selective</td>
<td>Mutated and wild-type FLt3</td>
<td></td>
<td>Weakness</td>
</tr>
<tr>
<td>Quizartinib (AC220)</td>
<td>Selective</td>
<td>Mutated and wild-type FLt3</td>
<td></td>
<td>Prolongation</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>Selective</td>
<td>Mutated and wild-type FLt3</td>
<td></td>
<td>Fatigue, diarrhea</td>
</tr>
<tr>
<td>Midostaurin (PD180,984)</td>
<td>Selective</td>
<td>Mutated and wild-type FLt3</td>
<td></td>
<td>Diarrhea, unusual muscle cramps, bruising</td>
</tr>
<tr>
<td>Gilteritinib (ASP2215)</td>
<td>Selective</td>
<td>FLT3/AXL</td>
<td>Phase I/II [50]</td>
<td>Diarrhea, fatigue, high liver function tests (LFT)</td>
</tr>
</tbody>
</table>

INSTEAD – A SINGLE STUDY

7 & 3, HIDAC consolidation +/-

- Midostaurin
- Quizartinib
- Crenolonib
- Gilteritinib
- Sorafenib

Standard definition of FLT3 + (stratify by VAF)
Compare flow and pcr MRD
All ages
Standardize “intent to transplant” language
OS, ?? EFS endpoint
Gemtuzumab ozogamicin (GO)

Humanized murine anti CD33 monoclonal antibody (hP67.6) conjugated to NAc-calicheamicin
Addition of GO to Chemotherapy for Younger AML Patients Does NOT Improve OS or EFS (MRC AML 15 Trial)

Burnett et al. J Clin Oncol 2011;29:369
Addition of Fractionated GO to 3+7 Induction and Consolidation in Older AML Patients Improves EFS and OS

Addition of GO to Induction Chemotherapy for AML:
A Meta-Analysis of Data from 3325 Individual Patients

ARE YOU CONFUSED?

- Polymorphism assay is not routinely available
- Dose and schedule are all over the place
- We use GO in CBF leukemias à la Français – days 1, 4, 7
- Not for high risk cytogenetics
- There may be benefit in FLT3 +
Effect of gilteritinib on survival in patients with FLT3-mutated (FLT3mut+) relapsed/refractory (R/R) AML who have common AML co-mutations or a high FLT3-ITD allelic ratio.

M Levis, A Perl, G Martinelli, et al

• Phase 3 - Gilteritinib vs chemotherapy
• CR + CRh : 34% (21% CR) vs ~ 15%
• Med OS : 9.3 vs 5.6 mos
• Survival @ 12 mos: 37% vs 16.7%
• Phase 3 in progress : 3 & 7 +/- Gil
Two-sided *p*-values were determined according to the log-rank test; the Kaplan-Meier method in combination with the Greenwood formula were used to determine overall survival and corresponding 95% confidence intervals.

Abbreviations: CI, confidence interval; HR, hazard ratio; HSCT, hematopoietic stem cell transplantation; ITT, intention-to-treat; OS, overall survival.

OVERALL SURVIVAL WITH CENSORING AT TRANSPLANTATION
(ITT POPULATION: N=371)

Median OS (95% CI)
8.3 months (6.7, 10.2)

HR=0.575 (95% CI: 0.434, 0.762); *p*=0.0001
Ivosidenib (IVO; AG-120) in mutant IDH1 relapsed/refractory acute myeloid leukemia (R/R AML): Results of a phase 1 study

Daniel A Pollyea1, Courtney D DiNardo2, Stéphane de Botton2, Eytan M Stein4, Gail J Roboz5, Alice S Mims6, Ronan T Swords7, Jessica K Altman8, Robert H Collins9, Gabriel N Mannis10, Geoffrey L Uy11, Will Donnellan12, Arnaud Pigneux13, Amir T Fathi14, Hua Liu15, Bin Wu15, Eyal C Attar15, Martin S Tallman4, Richard M Stone,16 Hagop M Kantarjian2

1University of Colorado School of Medicine, Aurora, CO; 2University of Texas MD Anderson Cancer Center, Houston, TX; 3Institut Gustave Roussy, Villejuif, France; 4Memorial Sloan Kettering Cancer Center, New York, NY; 5Weill Cornell Medical College, New York, NY; 6Ohio State University Wexner Medical Center, Columbus, OH; 7Sylvester Comprehensive Cancer Center, Miami, FL; 8Northwestern University, Chicago, IL; 9UT Southwestern Medical Center, Dallas, TX; 10UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, CA; 11Washington University School of Medicine, St Louis, MO; 12Sarah Cannon Research Institute, Nashville, TN; 13CHU Bordeaux, Bordeaux, France; 14Massachusetts General Hospital Cancer Center, Boston, MA; 15Agios Pharmaceuticals, Inc., Cambridge, MA; 16Dana-Farber Cancer Institute, Boston, MA
# Response in R/R AML 500 mg (n=179)

<table>
<thead>
<tr>
<th>CR+CRh rate, n (%) [95% CI]</th>
<th>R/R AML 500 mg (n=179)</th>
<th>Overall Response Rate, n (%) [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to CR/CRh, median (range) months</td>
<td>2.0 [0.9, 5.6]</td>
<td>1.9 [0.8, 4.7]</td>
</tr>
<tr>
<td>Duration of CR/CRh, median [95% CI] months</td>
<td>8.2 [5.6, 12.0]</td>
<td>6.5 [5.5, 10.1]</td>
</tr>
<tr>
<td>CR rate, n (%) [95% CI]</td>
<td>43 (24.0) [18.0, 31.0]</td>
<td></td>
</tr>
<tr>
<td>Time to CR, median (range) months</td>
<td>2.8 [0.9, 8.3]</td>
<td></td>
</tr>
<tr>
<td>Duration of CR, median [95% CI] months</td>
<td>10.1 [6.5, 22.2]</td>
<td></td>
</tr>
<tr>
<td>CRh rate, n (%)</td>
<td>14 (7.8)</td>
<td></td>
</tr>
<tr>
<td>Duration of CRh, median [95% CI] months</td>
<td>3.6 [1.0, 5.5]</td>
<td></td>
</tr>
</tbody>
</table>

CRh = 9 patients with investigator-assessed responses of CRi/CRp and 5 with MLFS

Among the 179 patients with R/R AML, 5 from dose escalation and 1 from dose expansion were not positive for mIDH1 by the companion diagnostic test and none of these 6 patients achieved a CR or CRh
CR+CRh was consistent across baseline age groups, including patients who were > 65 years of age
Overall response rate includes CR, CRi/CRp, MLFS and PR

Data cutoff: 10Nov2017. PD, progressive disease; PR, partial response

Presented By Daniel Pollyea at 2018 ASCO Annual Meeting
Overall Survival by Best Response in R/R AML 500 mg (n=179)

Presented By Daniel Pollyea at 2018 ASCO Annual Meeting

Number of patients at risk:

<table>
<thead>
<tr>
<th>Overall survival (months)</th>
<th>CR+CRh</th>
<th>Non-CR/CRh responders</th>
<th>Non-responders</th>
</tr>
</thead>
<tbody>
<tr>
<td>57</td>
<td>57</td>
<td>57</td>
<td>56</td>
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<tr>
<td>50</td>
<td>43</td>
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<td>15</td>
<td>14</td>
</tr>
<tr>
<td>1</td>
<td>104</td>
<td>57</td>
<td>55</td>
</tr>
</tbody>
</table>

Non-CR/CRh responders include CRi, CRp, and MLFS who are not CRh
Non-responders = all others including those with best responses of SD, PD, or not evaluable

Data cutoff: 10Nov2017  NE, not estimable
TAKE HOME – IDH1 and IDH2

• Do molecular testing on all AML/MDS
• Responses can be slow
• Differentiation syndrome
• Almost certainly palliative
• Trials in combination with chemotherapy are in progress
Minimal Residual Disease

- Detectable by flow, pcr with $>10^{-4}$ sensitivity
- In general, predictive of relapse and inferior outcome
- Can now study the characteristics of single, sorted cells
Association between pretransplant disease status and outcome for patients with acute myeloid leukemia (AML) after myeloablative hematopoietic cell transplantation (HCT).

Daisuke Araki et al. JCO 2016;34:329-336
## Response Rates

<table>
<thead>
<tr>
<th></th>
<th>Aza/Venetoclax</th>
<th>Azacytidine</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>37%</td>
<td>18%</td>
</tr>
<tr>
<td>CCR</td>
<td>66%</td>
<td>28%</td>
</tr>
</tbody>
</table>
Azacitidine and Venetoclax in Previously Untreated Acute Myeloid Leukemia


Promoting Apoptosis with Venetoclax — A Benefit for Older Patients with AML

Charles A. Schiffer, M.D.
Median follow-up, 20.5 mo (range, <0.1–30.7)
Hazard ratio, 0.66 (95% CI, 0.52–0.85)
P<0.001

No. at Risk
Azacitidine plus venetoclax
Azacitidine plus placebo

<table>
<thead>
<tr>
<th>Months</th>
<th>Azacitidine plus venetoclax</th>
<th>Azacitidine plus placebo</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>286</td>
<td>145</td>
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<tr>
<td>3</td>
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<td>0</td>
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<tr>
<td>33</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
MANY REMAINING QUESTIONS

• Definition of “unfit for chemotherapy”
• Should this replace 7 & 3 for older patients?
• Unproven in CBF AML where HIDAC is important for cure
• Untested in “proliferative” AML

The principle of synergy has been established

• How to build upon these results
  – In combination with FLT3, IDH inhibitors
  – In combination with standard chemotherapy
WHY ARE SOME PATIENTS CURED?

• Sufficient cytoreduction by chemotherapy
• Unique sensitivity of the clonogenic leukemia stem cell (CBF AML)
• Re-expression of genes suppressed by the CBF or other mutations
• Differentiation of leukemia: “clonal remissions"
• Recovery of immune surveillance – elimination/suppression of residual disease