Personalized Therapy for Acute Myeloid Leukemia

Patrick Stiff MD
Loyola University Medical Center
708-327-3216
Major groups of Mutations in AML

- AML genomes have fewer mutations than most other adult cancers (on average: 13, five of which are among the 23 recurrently mutated genes)
- Nine key categories:
  - Transcription-factor fusions (18%)
  - Gene encoding nucleophosmin (*NPM1*) (27%)
  - Tumor-suppressor genes (16%)
  - DNA-methylation-related genes (44%)
  - Signaling genes (59%)
  - Chromatin-modifying genes (30%)
  - Myeloid transcription-factor genes (22%)
  - Cohesin-complex genes (13%)
  - Spliceosome-complex genes (14%)

Targets for AML: Is this Achievable?

- Chronic Myeloid Leukemia: 1 target
  - Bcr-abl
- Acute Myeloid Leukemia: many targets

<table>
<thead>
<tr>
<th>Unfavorable recurrent genetic abnormalities</th>
<th>Unfavorable overexpression of single genes</th>
</tr>
</thead>
<tbody>
<tr>
<td>• IDH1, IDH2</td>
<td>• BAALC</td>
</tr>
<tr>
<td>• WT1</td>
<td>• ERG</td>
</tr>
<tr>
<td>• MLL-PTD</td>
<td>• EVI1</td>
</tr>
<tr>
<td>• NRAS</td>
<td>• MN1</td>
</tr>
<tr>
<td>• KRAS</td>
<td></td>
</tr>
<tr>
<td>• TP53</td>
<td></td>
</tr>
<tr>
<td>• TET2</td>
<td></td>
</tr>
<tr>
<td>• ASXL2</td>
<td></td>
</tr>
<tr>
<td>• RUNX1</td>
<td></td>
</tr>
<tr>
<td>• DNMT3A</td>
<td></td>
</tr>
</tbody>
</table>
AML Genetic Mutations

DNA methylation (46%): DNMT3A, TET2, IDH
Chromatin modifiers (30.5%): ASXL1, EZH2, MLL fusions

Splicosome mutations (13.5% in AML, up to 85% in MDS)
Splice site mutations associated with epigenetic mutations: SF3B1 and DNTM3A, SRSF2 and TET2, U2AF35 and ASXL1

IDH mutations → “oncometabolite” 2-HG
Metabolic input through acetyl-CoA and SAM → cofactors for methylation/acylation

Activated signaling: FLT3, KIT, KRAS/NRAS (59%)
Myeloid TF: RUNX1, CEBPa, EVI1 (22%)
TF fusions: PML-RARA, MYH11-CBFβ, RUNX1-RUNX1T1 (18%)

TF fusions aberrantly recruit DNMTs and HDACs → silencing of genes

Epigenetic alterations silence antigen processing and presentation (TAA, MHC-I/II, CD40)

Epi genetics

Proliferation \[\uparrow\]
Differentiation \[\downarrow\]

Evading growth suppressors/Resisting cell death

Immune system/Inflammation

Metalic dysregulation

Genome instability/splice site mutations

DNA methylation (46%): DNMT3A, TET2, IDH
Chromatin modifiers (30.5%): ASXL1, EZH2, MLL fusions

TP53, WT1, PHF6 (16.5%)
NPM1 and ARF (27%)

Tumor suppressor genes are abnormally methylated → silenced in AML
Current Guidelines for Cytogenetic/Molecular Testing in AML: NCCN

• NCCN, January 2017: Diagnosis of AML requires baseline mutational testing with cytogenetics (karyotype +/- FISH) and molecular analyses for KIT, FLT3-ITD, NPM1, CEBPA, and other mutations

• These specific mutations chosen because:
  – Validated commercial assays available
  – Important for prognostication in subset of patients

# Importance of AML Mutations and Chromosome Abnormalities

<table>
<thead>
<tr>
<th>Genetic group</th>
<th>Subsets</th>
</tr>
</thead>
</table>
| **Favorable** | t(8;21)(q22;q22); *RUNX1–RUNX1T1*  
inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB–MYH11*  
Mutated *NPM1* without *FLT3–ITD* (normal karyotype)  
Mutated *CEBPA* (normal karyotype) |
| **Intermediate-I†** | Mutated *NPM1* and *FLT3–ITD* (normal karyotype)  
Wild-type *NPM1* and *FLT3–ITD* (normal karyotype)  
Wild-type *NPM1* without *FLT3–ITD* (normal karyotype) |
| **Intermediate-II** | t(9;11)(p22;q23); *MLLT3–MLL*  
Cytogenetic abnormalities not classified as favorable or adverse† |
| **Adverse** | inv(3)(q21q26.2) or t(3;3)(q21;q26.2); *RPN1–EVI1*  
t(6;9)(p23;q34); *DEK–NUP214*  
t(v;11)(v;q23); *MLL* rearranged  
−5 or del(5q); −7; abnl(17p); complex karyotype† |
Frequencies of the Most Common Genetic Mutations in AML

- CEBPA+ 5.7%
- CEBPA+/MLL-PTD+ 1.2%
- FLT3-TKD+/MLL-PTD+ 0.8%
- FLT3-TKD+ 2.4%
- FLT3-ITD+/CEBPA+ 1.6%
- FLT3-ITD+/MLL-PTD+ 2.4%
- FLT3-ITD+ 8.1%
- NPM1+/FLT3-TKD+/CEBPA+ 0.4%
- NPM1+/FLT3-ITD+/CEBPA+ 0.4%
- NPM1+/FLT3-TKD+/CEBPA+ 1.2%
- NPM1+/FLT3-ITD+/CEBPA+ 1.2%
- NPM1+/FLT3-ITD+/FLT3-TKD+ 1.2%
- NPM1+/CEBPA+ 3.7%
- 4.5% MLL-PTD+
- 23.6% WT
- 19.5% NPM1+
- 17.9% NPM1+/FLT3-ITD+
- 4.1% NPM1+/FLT3-TKD+
Genetic Mutations in Luekemia

• So for CML with one major mutation:
  – Effective if not curative therapy with oral TKIs for the bcr/abl mutation: Gleevec®, Dasatinib®, Nilotinib®

• And for AML:
  – Unlikely that any one targeted agent will ever cure a single patient due to most patients having multiple mutations
  – The number of potentially actionable mutations is so large that no one therapy will be effective for more than 30% of any group of AML patients
Genetic Mutations do Not Occur in Isolation in AML
Strategy of Targeted Therapy for AML

- Targeted antibody-chemotherapy agents
- Targeted genetic therapy
Targeted Antibodies to AML Blasts: CD33

- CD33 is on most AML blasts, but not on stem cells
- Attaching a chemotherapy drug to an antibody permits more targeted damage to AML blasts
Mylotarg History

- Mylotarg was approved in the US under accelerated approval in May 2000 as monotherapy for patients with CD33+ Acute Myeloid Leukemia (AML) in 1st relapse who were ≥60 years old.

- Confirmatory trial – SWOG S0106 failed to confirm the clinical benefit of Mylotarg.

- Recognition of increased risk of veno-occlusive disease (VOD) in patients receiving Mylotarg in the post-marketing setting.

- Pfizer voluntarily withdrew Mylotarg from the US market in 2010.
**SWOG S0106:**

**Study Design**

- **Induction**
  - DNR 45 mg/m² + AraC + Mylotarg 6 mg/m²
  - N=295
  - If CR

- **Consolidation 3 Cycles**
  - AraC
  - N=300

- **Post-Consolidation**
  - Mylotarg 5 mg/m²
  - N=85
  - 3 cycles
  - Observation
  - N=84

**Objectives**

- CR Rate
- DFS

---

**SWOG S0106:**

**Interim Analysis August 2009**

<table>
<thead>
<tr>
<th></th>
<th>Mylotarg</th>
<th>Control</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Remission Rate, %</td>
<td>69</td>
<td>70</td>
<td>0.59</td>
</tr>
<tr>
<td>Median DFS, months</td>
<td>14</td>
<td>NR</td>
<td>-</td>
</tr>
<tr>
<td><strong>Hazard Ratio (95% CI)</strong></td>
<td><strong>1.48</strong></td>
<td><strong>(0.99, 2.22)</strong></td>
<td><strong>0.97</strong></td>
</tr>
<tr>
<td>Induction deaths</td>
<td>5.5</td>
<td>1.4</td>
<td><strong>0.0062</strong></td>
</tr>
</tbody>
</table>

**Conclusion**

- SWOG DSMC recommended early closure of both the induction and post-consolidation randomization
However a European trial used lower doses given more frequently with success.
Mylotarg® is now re-approved for the Initial Therapy of AML

Mylotarg in Patients with Previously Untreated De Novo AML

- Mylotarg in lower fractionated doses added to standard chemotherapy provides
  - Statistically significant and clinically meaningful improvement in EFS and RFS in both ALFA-0701 and the IPD meta-analysis
  - Clinically meaningful improvement in OS in ALFA-0701 confirmed by the IPD meta-analysis, where it was statistically significant

Subsequent Analyses showed that the greatest benefit for Mylotarg is in the favorable cytogenetic population with almost no benefit in the poor cytogenetic risk population

So Mylotarg: targeted agent that improves survival is favorable risk AML
Strategy of Targeted Genetic-Based Therapy for AML

• Start with the prognostically ‘bad’ genes
• Start with the most common genes
  – NPM1
  – CEBPA
  – FLT-3 ITD
  – IDH-1 and IDH-2
  – WT1
  – MLL-PTG
FLT-3

- Found on chromosome 13q12
- Proto-oncogene
- Encodes for a surface receptor: cytokine receptor
- Normally seen on early BM stem cells and cells that become myeloid (neutrophils) and lymphoid cells
- Critical factor for the proliferation and survival of stem cells: good for normal bone marrow cell growth; bad if there is no control mechanism for this growth
- Patients frequently with this mutation have very fast growing AMLs and high blood counts
- Overall about 30-40% of adults with AML have this mutation
Prognosis of FLT3 Mutations in AML

FLT3 Mutation Categories

Internal tandem duplications (FLT3 ITD)
- Found in up to 30% of AML - mostly in normal karyotypes
- Unfavorable prognosis (high relapse risk, decrease DFS and OS)

Point mutation in tyrosine kinase domain (FLT3-TKD)
- 7% of AML
- Point mutations and small deletions mostly of codons 835 and 836
Treatment of Patients with FLT3 ITD Mutations in AML

- **Midostaurin**, a multitargeted kinase inhibitor, was originally developed as a protein kinase C inhibitor for treatment of patients with solid tumors.
- On the basis of preclinical studies, which showed synergy between chemotherapy and midostaurin, a phase 1b study involving patients with newly diagnosed AML was conducted.
- The study established that oral midostaurin could be administered safely (with an acceptable side-effect profile) at a dose of 50 mg twice daily for 14 days, beginning on the eighth day after the start of treatment during courses of induction and consolidation chemotherapy, and that this regimen had encouraging efficacy in patients with a FLT3 mutation.

August 3, 2017
Treatment of Patients with FLT3 ITD Mutations in AML: **Midostaurin**

So overall a survival advantage for the group that received the Midostaurin

This drug is now FDA approved for this indication

This therapy helped survival in BMT and non-BMT patients

BMT is still the optimal way to treat these patients in remission—so this drug is not a substitute for transplant

**Figure 2. Overall Survival.**

Treatment of Patients with FLT3 ITD Mutations in AML

Other FLT3 Drugs for AML—all are oral agents:

• **Sorafenib**: (FDA approved for kidney cancer)
• **Quizartinib**: experimental
• **Crenolanib**: experimental
• **Gilteritinib**: experimental

For all clinical trials are ongoing and preliminary results are very encouraging: recent updates
Treatment of Patients with FLT3 ITD Mutations in AML

• For Gilteritinib the treatment of patients with refractory FLT3+ AML in one such trial was successful.

• This was their sole therapy

• Of the 249 patients included in the full analysis, 40% had a response to treatment including 90% of the responders with a complete disappearance of the leukemia.

• 25 (10%) had partial remission.

FDA Approval Sought for Gilteritinib in FLT3+ AML
Published: Tuesday, Apr 24, 2018
Treatment of Patients with FLT3 ITD Mutations in AML

Tokyo, Munich, and Basking Ridge, NJ – (May 8, 2018) – Daiichi Sankyo Company, Limited (hereafter, Daiichi Sankyo) announces that the pivotal QuANTUM-R phase 3 study of single agent quizartinib met its primary endpoint of significantly prolonging overall survival compared to salvage chemotherapy in patients with relapsed/refractory acute myeloid leukemia (AML) with FLT3-ITD mutations after first-line treatment with or without hematopoietic stem cell transplantation (HSCT)
Treatment of Patients with FLT3 ITD Mutations in AML

• Effect of Cytarabine/Anthracycline/Crenolanib Induction on Minimal Residual Disease (MRD) in Newly Diagnosed FLT3 Mutant AML

• 18/24 in complete remission at a medical follow-up of 8 months in first study

• 83% had achieved a minimal disease negative state; 80% of these had not relapsed

JCO: June 2017
Treatment of Patients with FLT3 ITD Mutations in Refractory AML: Summary of Single Agent Use

<table>
<thead>
<tr>
<th>Agent</th>
<th>Single agent activity</th>
<th>Response duration</th>
<th>Resistance mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sorafenib</td>
<td>ORR 92% (N = 12/13 with 6 CRi, 6 nCRi)</td>
<td>Median 72 days</td>
<td>Possibly expression of ALDH1A1, JAK3, and MMP15. TKD mutation at D835.</td>
</tr>
<tr>
<td>Quizartinib</td>
<td>CRc 48% (N = 92/191)</td>
<td>Median 79 and 89 days in two cohorts</td>
<td>Mutated C/EBPα or TKD mutation at F691 or D835</td>
</tr>
<tr>
<td>Midostaurin</td>
<td>2% PR (N = 1/35)</td>
<td>60 days</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

**Blood Reviews**: *Volume 29, Issue 1*, 2015
IDH-2 Mutations in AML: Therapy

- **Enasidenib** (AG-221/CC-90007) is a first-in-class, oral, selective inhibitor of mutant-IDH2 enzymes.
- A phase 1/2 study assessed the clinical activity of enasidenib in patients with mutant-\textit{IDH2} advanced myeloid malignancies.
- Patients with relapsed or refractory AML (n=176) were treated with this oral agent alone.
- Overall response rate was 40.3%, with median response duration of 5.8 months. Responses were associated with cellular differentiation and maturation, typically without evidence of aplasia.
- Median overall survival among relapsed/refractory patients was 9.3 months, and for the 34 patients (19.3%) who attained complete remission the overall survival was 19.7 months.
- Based on these results the FDA has approved this agent for use in patients with IDH-2 mutations who fail initial therapy.

Blood, 2017
Other New Targeted Agents in AML

• IDH-2 mutated AML
• Novel targeted hypomethylating agents
• BCL-2 targeted agents
Novel Hypomethylating Agents

• Guadecitabine (SGI-110) is a new agent that is a prodrug of decitibine which among other attributes leads to a longer half life when administered

• The first was a study of 103 patients with relapsed/refractory AML In this study, 23% of patients had CR, CRp, or Cri. The median survival was 6.6 months, and 19% of patients were alive at 2 years.

• A second trial in 51 untreated AML patients who were ineligible for intensive induction showed a 57% CR/CRp/CRi and a median survival of 10.5 months.

Novel Hypomethylating Agents

• DNA “methylation” is the modification of DNA by adding a methyl group to it which determines the use of DNA for cell growth and differentiation to normal blood cells.

• Too much methylation leads to abnormal cell growth and survival longer than normal cells, seen in particular in AML.

• Hypomethylating agents decrease the amount of cellular DNA methylation and disrupt these patterns.

• The main hypomethylating agents used to treat AML are azacitidine and decitibine.

NEJM, 2003
BCL2 Mutations

• BCL-2 is overexpressed in most B cell lymphomas and CLL
• When overexpressed, cells do not grow faster, they die slower
• This slowing of death also occurs in AML, although BCL-2 is not usually overexpressed in AML
• However, inhibiting the normal functions of BCL2 in the lab in AML cells did promote their killing
• Venetoclax, the FDA approved BCL2 inhibitor, did show a modest effect when used as a single agent in AML, a complete remission rate of 19%
BCL2 Inhibition: Venetoclax in Combination with Hypomethylating Agent: Impressive Preliminary Results

CR rate: 66%
Average survival 17.5 months

Decitibine alone: same patients
CR rate: 14%
Average survival 7.7 months

“If phase 3 testing shows a clinical benefit of venetoclax combined with low-dose chemotherapy or HMAs, then this combination would not only redefine therapeutic approaches to AML in older patients unfit for intensive chemotherapy, but would also likely prompt expanded testing of the venetoclax combinations in younger patients treated with curative intent” Blood Advances, 2017
Personalized Therapy for AML

• Newer targeted agents just in the last 12 months are showing an improvement in survival for AML—for the first time in 40 years we are seeing more patients live longer. New FDA approvals are finally here.

• It is critical to know not only the chromosome but also the genetic make-up of each patient’s AML to design the best therapy

• Like other cancers, the first treatment(s) remain the best opportunity for the best outcome—knowing as much about the leukemia when first diagnosed will provide the best chance for cure