Clinical Application of Personalized Medicine for Acute Myeloid Leukemia

Joon-ho Moon, MD, PhD
Dept. of Hematology/Oncology
Kyungpook National University Hospital
I have no personal or financial interests to declare:

I have no financial support from an industry source at the current presentation.
Personalized Medicine for AML

- Picking the right drug or correctly characterizing the malignant clone, and picking the right treatment for the right patient at the right time
- This process requires monitoring for changes in disease burden and biology over time.
- Which require …
  - Germline genetic factors and tumor associated somatic mutations
  - Correlation of biomarkers with response to agents
  - Measurements of post-treatment residual disease burden and biology

1. Standard of care & challenges of AML
2. Classification & risk groups
3. Risk assessment by minimal residual disease
4. Individualized approaches for AML
3+7 regimen: Options for Improvement?

- 3+7 regimen has been standard of care for more than 20 decades.
- To reduce the risk of relapse, there have been many efforts to optimize the doses of chemotherapy.
- Remission does not mean the disease has been cured, but rather that it cannot be detected with conventional diagnostic methods.
- The likelihood of achieving and maintaining clinical remission depends on prognostic features of the original leukemia.

Challenges of AML

- By cytogenetic analysis, 40-50% of patients with AML present with normal karyotypes (NK), with extremely variable clinical outcomes.
- Molecular profiling revealed heterogeneous sub-groups of NK-AML.
1. Standard of care & challenges of AML
2. Classification & risk groups
3. Risk assessment by minimal residual disease
4. Individualized approaches for AML
AML is genetically diverse and clonally heterogenous

- Analysis of 200 de novo AML patients according to WGS or WES identified an excess of 200 recurrently mutated genes
- 23 genes were significantly mutated
- Most patients have 2 or more acquired mutations and are clonally represented

Ley et al. NEJM 2013;368:2059
In the earlier studies, the mutational status of \textit{NPM1}, \textit{FLT3-ITD}, \textit{CEBPA} are associated with the treatment outcomes for patients with NK-AML.

Schlenk et al. NEJM 2008;358:1909
DNA methyltransferases (DNMTs) are key enzymes in the epigenetic regulation of gene expression. "DNMT3A mutations have been reported in 18-22% of patients with AML. R882 is the most commonly mutated residue. Data concerning the prognostic significance of DNMT3A mutations have been conflicting."
Non–R882-DNMT3A mutations are associated with adverse prognosis in younger patients.

**DNMT3A-R882MUT** is a significant prognostic factor for inferior transplantation survival outcome even after allo-HCT.
## ELN updated recommendation

<table>
<thead>
<tr>
<th>Risk Category*</th>
<th>Genetic Abnormality</th>
</tr>
</thead>
</table>
| **Favorable**  | t(8;21)(q22;q22.1); *RUNX1-RUNX1T1*  
inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*  
Mutated *NPM1* without *FLT3-ITD* or with *FLT3-ITD*<sup>low</sup>†  
Biallelic mutated *CEBPA* |
| **Intermediate** | Mutated *NPM1* and *FLT3-ITD*<sup>high</sup>†  
Wild-type *NPM1* without *FLT3-ITD* or with *FLT3-ITD*<sup>low</sup>† (without adverse-risk genetic lesions)  
t(9;11)(p21.3;q23.3); *MLLT3-KMT2A*‡  
Cytogenetic abnormalities not classified as favorable or adverse |
| **Poor/Adverse** | t(6;9)(p23;q34.1); *DEK-NUP214*  
t(v;11q23.3); *KMT2A* rearranged  
t(9;22)(q34.1;q11.2); *BCR-ABL1*  
inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2,MECOM(EVI1)*  
-5 or del(5q); -7; -17/abn(17p)  
Complex karyotype,§ monosomal karyotype||  
Wild-type *NPM1* and *FLT3-ITD*<sup>high</sup>†  
Mutated *RUNX1*¶  
Mutated *ASXL1*¶  
Mutated *TP53*# |
Role of Allo-HCT in $NPM1^{WT}/FLT3$-ITD$^{Neg/Low}$

- $NPM1^{mut}/FLT3$-ITD$^{neg}$ or $CEBPA^{dm}$
- $NPM1^{WT}/FLT3$-ITD$^{neg}$ /non-$CEBPA^{dm}$
- FLT3-ITD$^{pos}$/non-$CEBPA^{dm}$

Contents

1. Standard of care & challenges of AML
2. Classification & risk groups
3. Risk assessment by minimal residual disease
4. Individualized approaches for AML
Minimal Residual Disease in AML

- Genetic landscape of adult AML has been recently unraveled.
- Due to their genetic heterogeneity, only a handful of markers are currently used for the evaluation of MRD.
- Detailed sequential information regarding the amount of disease remaining to treat is going to be as important as the type of disease.
- Useful
  - In determining the length of treatment and the need for additional therapy after completion of standard treatment.
  - The type of treatment based on the kinetics of disease reduction as a marker of therapeutic efficacy.
  - The clonal composition of residual leukemia during or after treatment may provide predictive information about the response or resistance to a therapy.

NGS has proven its prognostic and diagnostic potentials, thus has been being incorporated into clinical practice in AML.

Application of NGS could improve a prognostic stratification of outcomes after allogeneic HCT in AML.

In our study, we aim to answer following questions:
- Can NGS stratify prognosis of recipients after allogeneic HCT in AML?
- Can Early NGS-based monitoring at day 21 of post-HCT predict post-transplant relapse?
- Can NGS help identify dynamic changes of leukemic clone after allogeneic HCT?

Kim TH et al. Blood 2018;132:1604
**Methods**

- BM/PB samples sequenced in this study are taken at time of diagnosis, pre-HCT, post-HCT (day 21), longer follow up (3, 6, 12 months), and/or relapse.

- Using Agilent custom probe set targeting 84 myeloid gene panel, we sequenced 529 samples using Illumina HiSeq 2500.

- Read processing and variant calling were performed as in our previous study\(^1\)

---

Mutation dynamics over the course of treatments

- 256 mutations in 90 patients (86.5%, n=90/104) were captured at diagnosis.
- \( \text{FLT3} (38.5\%), \text{DNMT3A} (25.0\%), \text{NPM1} (22.1\%), \text{IDH2} (14.4\%) \) and, \( \text{CEBPA} (14.4\%) \) were commonly mutated.

Kim TH et al. Blood 2018;132:1604
Presence of allelic burden at day 21 post-HCT is associated with worse OS and higher relapse

- Post-HCT VAF at day 21 (over 0.2%) was an independent prognostic factor for OS (HR 3.07) and relapse risk (HR 4.75) after allogeneic HCT.

Kim TH et al. Blood 2018;132:1604
VAF<sup>0.2%+-Post-HCT<sup>D21</sup> can further stratify intermediate and adverse risk group for OS and relapse

Kim TH et al. Blood 2018;132:1604
Detection of Mutations at Diagnosis and CR

Jorgen-Lavrencic et al. NEJM 2018;378:1189
Detection of DTA mutations have no prognostic value

Detection of DTA mutations

Cut off ≤ 5%

Solid line: DTA detectable
Dashed line: DTA not detectable

Cut off ≤ 2.5%

Relapse among patients with persistent DTA mutations

Jorgen-Lavrencic et al. NEJM 2018;378:1189
Rates of Relapse and Overall Survival

B  Relapse among All Patients

C  Overall Survival among All Patients

Jorgen-Lavrencic et al. NEJM 2018;378:1189
1. Standard of care & challenges of AML
2. Classification & risk groups
3. Risk assessment by minimal residual disease
4. Individualized approaches for AML
Clearance of *TP53* mutations with Decitabine

- *TP53* mutation has known to be resistance to conventional chemotherapy
- Patients with AML and MDS who had unfavorable cytogenetic abnormalities, *TP53* mutations, or both had robust mutation clearance after receiving serial 10-day courses of decitabine

Welch et al. NEJM 2016;375:2023
**TP53** mutation had a response to **decitabine** but short-lived.

---

**D** Survival According to TP53 Mutation

**F** Survival after Stem-Cell Transplantation According to TP53 Mutation

---

Welch et al. NEJM 2016;375:2023
Molecular profiling contribute to identify patients with distinct biological subgroups.

This approach is likely to help identify patients who will respond best to particular therapies and improve our understanding of AML.

Assessment of MRD at certain time point will allow modification of our therapeutic approaches.

Challenges are on-going how to use molecular markers to deliver patient-tailored clinical decision.
Acknowledgement

- Chonnam National University
  - Dr. Hyeoung Joon Kim
  - Dr. Jae-Sook Ahn
  - Dr. Seung Hyun Choi
  - Ms. Jayeon Lee
  - Dr. Jae Jung Lee
  - Dr. Deok Hwan Yang
  - Dr. Seo-Yeon Ahn
  - Dr. Sung Hoon Jung

- Kyungpook National University
  - Dr. Joon Ho Moon
  - Dr. Sang Kyun Sohn
  - Dr. Yoo Jin Lee

- Princess Margaret Cancer Centre
  - Dr. Dennis (Dong Hwan) Kim

- University of Toronto
  - TaeHyung Kim
  - Dr. Zhaolei Zhang

- Soonchunhyang University Bucheon Hospital
  - Dr. Seong Kyu Park
Thank you!