Impact of New Diagnostic Markers on Treatment Decisions in Acute Myeloid Leukemia

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Genetic Diversity of AML

45% normal karyotype
5% t(8;21)
6% inv(16)
2% t(9;11)
2% t(11q23)
1% t(6;9)
1% inv(3)/t(3;3)

11% complex karyotype

23% various
e.g. -5/5q-, -7, 7q-, +8, 9q-, +13, 20q-

excl. APL

Survival According to Cytogenetic Risk Group: 
*AMLSG Treatment Trials (16-60 yrs, n=1130)*

<table>
<thead>
<tr>
<th>Time (years)</th>
<th>Survival (%)</th>
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<tbody>
<tr>
<td></td>
<td>Favorable</td>
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<tr>
<td></td>
<td>Intermediate</td>
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<tr>
<td></td>
<td>Adverse</td>
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- inv(16); t(8;21); t(15;17)
- normal karyotype; all other
- inv(3); t(6;9); t(v;11q23)
- -5/5q-; -7; abn(17p); complex
Genetic Diversity of AML

NPM1, CEBPA, FLT3, RUNX1, MLL, RAS, WT1, IDH1/2, TET2, ASXL1
BAALC, ERG, EVI1, MN1, miRs

45% normal karyotype

KIT, RAS, FLT3, CBL

5% t(8;21)
6% inv(16)

2% t(9;11)
2% t(11q23)

1% t(6;9)

 FLT3  1% inv(3)/t(3;3)

11% complex karyotype

TP53, ?

23% various
e.g. -5/5q-, -7, 7q-, +8, 9q-, +13, 20q-


excl. APL
Normal karyotype AML

NPM1, CEBPA, FLT3-ITD, FLT3-TKD, MLL-PTD, RAS, WT1

Prognostic Impact of Genotypes in Younger Adults with CN-AML

Relapse-Free Survival

Overall Survival

Clinical Significance

Diagnosis

New provisional entities:
AML with mutated **NPM1**
AML with mutated **CEBPA**

Risk Stratification

**Fav**
- t(8;21)(q22;q22); **RUNX1-RUNX1T1**
- inv(16)(p13.1q22); **CBFB-MYH11**
Mutated **NPM1** without FLT3-ITD (nl karyotype)
Mutated **CEBPA** (nl karyotype)

**Int-I**
- Mutated **NPM1** and FLT3-ITD (nl karyotype)
- Wild type **NPM1** and FLT3-ITD (nl karyotype)
- Wild type **NPM1** without FLT3-ITD (nl karyotype)

**Int-II**
- t(9;11)(p22;q23); **MLLT3-MLL**;
cytogenetic abnormalities not classified as favorable or adverse

**Adv**
- inv(3)(q21q26.2) or t(3;3)(q21;q26.2); **RPN1-EVI1**
- t(6;9)(p23;q34); **DEK-NUP214**; t(v;11q23); **MLL** rearranged; -5 or del(5q); -7; abn(17p); complex karyotype (=3)


AML with Mutated CEBPA

Bi-allelic mutations in ~2/3 of cases (mostly N- and C-term)
Mono-allelic mutations in 1/3 of cases

Biological and clinical difference?

Study of 1182 cytogenetically normal AML patients (16-60 yrs)

- 193 patients from HOVON SAKK (Erasmus University)
- 989 patients from AMLSG cohort (University of ULM)
- CEBPA, FLT3\textsuperscript{ITD}, FLT3\textsuperscript{TKD}, NPM1, NRAS
Clinical Outcome in CEBPA Subgroups

![Graph showing cumulative proportion survival over time for different subgroups of CEBPA. The graph indicates that CEBPA<sup>dm</sup> and CEBPA<sup>sm</sup> have lower cumulative survival compared to CEBPA<sup>wt</sup>.]

- CEBPA<sup>dm</sup> versus CEBPA<sup>wt</sup>: \( P < 0.0001 \)
- CEBPA<sup>sm</sup> versus CEBPA<sup>wt</sup>: \( P = 0.05 \)
- CEBPA<sup>sm</sup> versus CEBPA<sup>dm</sup>: \( P = 0.06 \)
Unsupervised Gene Expression Analyses

Is $CEBPAdm$ a unique group in terms of GEP?

Is $CEBPAsm$ a unique group in terms of GEP?

Taskesen, Bullinger et al. Submitted.
Isocitrate Dehydrogenase (IDH)

- **Mutations first reported in malignant gliomas**
  - Glioblastoma multiforme (12%); particularly frequent in anaplastic astrocytoma, oligodendroglioma, sec. glioblastoma ($IDH1^{mut} \sim 70\%; \ IDH2^{mut} >3\%$)
  - Mutational cluster in exon 4: $IDH1^{mut}$ (R132), $IDH2^{mut}$ (R172)
  - Associated with younger age and better survival


- **Mutations in AML identified by sequencing a CN-AML genome**
  - $IDH1$ mutations found in 15/187 (8%) AML and strongly associated with normal karyotype AML (13/80; 16%); no $IDH2$ mutation found

Cancer-Associated *IDH* Mutations

IDH1

- IDH1<sup>R132 mut</sup>

IDH2

- IDH2<sup>R172K</sup>
- IDH2<sup>R140Q</sup>

2HG elevated in AML and glioblastomas

- Production of an oncogenic metabolite
- Inherited disorder: 2-hydroxyglutaric aciduria

Prognostic Impact of *IDH1* and *IDH2* Mutations in Cytogenetically Normal AML

Translation into Novel Therapies: AML with FLT3 Internal Tandem Duplication

- Found ~ 25% of adult patients with AML
- **Impact on prognosis: poor**
  
  Impact of mutant-to-wild type ITD allelic ratio
  

  **Impact of ITD insertion site (JM vs. TK-1 domain)**
  
  
  

- **Impact on therapy**
  
  -> evaluation of FLT3 inhibitors
  
  eg, PKC 412, CEP-701 (phase III); AC220 (phase II)
  
  -> allogeneic HSCT may improve outcome
Tyrosine Kinase Inhibitors: Selectivity and Potency

Phase III Study of Chemotherapy + Midostaurin (PKC412) or Placebo in Newly Diagnosed Patients ≥ 60 Years of Age with FLT3 Mutated Acute Myeloid Leukemia

CALGB, AMLSG, CETLAM, ECOG, EORTC, GIMEMA, NCIC, OSHO, PETHEMA, SAL, SWOG

Induction
Daunorubicin
Cytarabine
+ Placebo

Consolidation x4**
High-Dose Cytarabine
+ Placebo

Maintenance
Placebo

Daunorubicin
Cytarabine
+ PKC412

High-Dose Cytarabine
+ PKC412

PKC412

FLT3 ITD/TKD Mutation Screening Within 48 Hours*
n=514

*Patients may receive hydroxyurea during screening phase
**Patients with an HLA-compatible family donor may proceed to allogeneic HSCT

PI: Dr. R. Stone, CALGB
AML with Mutated \( K\!\!T \)

- Mutations mostly found in CBF AML
  - \( \text{inv}(16)(\text{p}13.1\text{q}22); \text{CBFB-My}h11 \) (30-35%)
  - \( \text{t}(8;21)(\text{q}22;\text{q}22); \text{Runx1-Runx1t1} \) (30-35%)

- Higher \( K\!\!T \) expression in CBF AML

- Impact on prognosis: in general poor

- Impact on therapy
  -> evaluation of KIT inhibitors
    eg, dasatinib, PKC412, CEP-701
Phase II Study of Chemotherapy + Dasatinib in Patients with Newly Diagnosed Core Binding Factor (CBF) AML - AMLSG 11-08

**Induction**
- CBF Mutation Screening Within 48 Hours
- Daunorubicin + Cytarabine + Dasatinib

**Consolidation x 4**
- High-Dose Cytarabine* + Dasatinib

**Maintenance**
- Dasatinib 1 year

All adult patients eligible for intensive therapy, no upper age limit

* Cytarabine: 18-60yrs: 3g/m², q12hr, d1-3; >60yrs: 1g/m², q12hr, d1-3

PI: H. Döhner, AMLSG [ClinicalTrials.gov Identifier: NCT00850382]
Log$_{10}$ Reduction of Fusion Gene Copy Ratios in Blood After Induction By Application of Dasatinib

AML with \textit{NPM1} Mutation

- Found in 25-35\% of AML (45-60\% of CN-AML)*
- Exon 12 mutations leading to cytoplasmic shift of protein*
- Immunophenotype
  \begin{itemize}
    \item High CD33 expression \textbf{(Low to absent CD34)}
  \end{itemize}
- Potential impact of ATRA as molecular therapy**

Phase III Study of Intensive Chemotherapy +/- ATRA
In Previously Untreated Patients >60 yrs with AML
AMLSG HD98B Trial

Beneficial Effect of ATRA Restricted to AML with $NPM1^{\text{mut}}/FLT3-\text{ITD}^{\text{neg}}$

ATRA and Survival in Younger Adult AML with \textit{NPM1} Mutation (AMLSG 07-04)

\textbf{Planned interim analysis 04-2009}
Phase III Study of Chemotherapy in Combination with ATRA with or without Gemtuzumab Ozogamicin (Mylotarg) in Patients with $NPM1^{\text{mut}}$ Acute Myeloid Leukemia

$\text{AMLSG 09-09 (active)}$

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**Induction x2**
- ATRA-ICE
- ATRA-ICE + GO

**Consolidation 1**
- ATRA Cytarabine**
- ATRA Cytarabine** + GO

**Consolidation 2+3**
- ATRA Cytarabine**

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**NPM1 Mutation**
**Screening Within 48 Hours***

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* All adult patients eligible for intensive therapy, no upper age limit
* Patients may receive hydroxyurea during screening phase
** Cytarabine: 18-60yrs: 3g/m$^2$, q12hr, d1-3; >60yrs: 1g/m$^2$, q12hr, d1-3

PL: R.F. Schlenk; Supported by Else Kröner-Fresenius-Foundation
AMLSG Genotype-Specific Treatment Trials

**Molecular Screening 24-48 hrs**

- **APL [t(15;17)] ~10%**
  - ATO+ATRA APL0406 GIMEMA / AMLSG / SAL

- **CBF AML ~13%**
  - Dasatinib AMLSG 11-08

- **AML FLT3mut ~25%**
  - PKC412 CALGB 10603 age <60
  - SU11248 AMLSG 10-07 age ≥60

- **AML NPM1mut ~17%**
  - ATRA +/- GO AMLSG 09-09

- **Other subtypes (mainly high-risk) ~35%**
  - Azacitidine + induction, Allo HSCT (1st priority), or HiDAC + AZA maintenance AMLSG 12-09
  - C-IARA (Clofarabine), Allo HSCT (or HiDAC) AMLSG 13-09
Acute Myeloid Leukemia in 2010

- Identification of novel genetic and epigenetic changes is facilitated by progress in genomics/epigenomics technology
- Cytogenetic and molecular diagnostics increasingly allow improved diagnosis, prognosis, and prediction
- Translation of molecular findings to clinic is increasing
  - 2008 WHO classification for de novo AML primarily based on genetic findings; >50% so classified (including provisional entities)
  - Clinical trials targeting patients with mutant tyrosine kinases and other molecules, or epigenetic abnormalities on-going
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