Hämatologie im Wandel 2017

Akute myeloische Leukämie: Behandlungsstrategien und Studien der AMLSG

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# 2017 ELN recommendations

<table>
<thead>
<tr>
<th>Risk category*</th>
<th>Genetic abnormality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favorable</td>
<td>t(8;21)(q22;q22.1); RUNX1-RUNX1T1</td>
</tr>
<tr>
<td></td>
<td>inv(16)(p13.1q22) or t(16;16)(p13.1;q22); CBFβ-MYH11</td>
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<tr>
<td></td>
<td>Mutated NPM1 without FLT3-ITD or with FLT3-ITD\textsuperscript{low}†</td>
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<tr>
<td></td>
<td>Biallelic mutated CEBPA</td>
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<tr>
<td>Intermediate</td>
<td>Mutated NPM1 and FLT3-ITD\textsuperscript{high}†</td>
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<tr>
<td></td>
<td>Wild-type NPM1 without FLT3-ITD or with FLT3-ITD\textsuperscript{low}† (without adverse-risk genetic lesions)</td>
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<tr>
<td></td>
<td>t(9;11)(p21.3;q23.3); MLLT3-KMT2A‡</td>
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<tr>
<td></td>
<td>Cytogenetic abnormalities not classified as favorable or adverse</td>
</tr>
<tr>
<td>Adverse</td>
<td>t(6;9)(p23;q34.1); DEK-NUP214</td>
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<tr>
<td></td>
<td>t(v;11q23.3); KMT2A rearranged</td>
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<td></td>
<td>t(9;22)(q34.1;q11.2); BCR-ABL1</td>
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<tr>
<td></td>
<td>inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); GATA2,MECOM(EVI1)\textsuperscript{−5 or del(5q); −7; −17/abn(17p)}</td>
</tr>
<tr>
<td></td>
<td>Complex karyotype§ monosomal karyotypell</td>
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<tr>
<td></td>
<td>Wild-type NPM1 and FLT3-ITD\textsuperscript{high}†</td>
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<tr>
<td></td>
<td>Mutated RUNX1†</td>
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<tr>
<td></td>
<td>Mutated ASXL1¶</td>
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<tr>
<td></td>
<td>Mutated TP53#</td>
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Döhner et al. Blood 2017
Translation into the clinic

Newly diagnosed AML

IC molecular screening
Registration AMLSG-BiO

→ AMLSG BiO-ID

BM&PB samples

→ Reference Lab
Overnight

Molecular screening

- PML-RARA
- RUNX1-RUNX1T1
- CBFβ-MYH11
- MLL-AF9
- FLT3-ITD
- FLT3-TKD
- NPM1
- CEBPA

Genotype adapted strategy

APL
CBF
NPM1\text{mut}
FLT3-ITD
...

0-8 hours

overnight

24-48 hours
Genotype adapted treatment strategies: AML with *NPM1* mutation

- Found in 25-35% of AML (45-60% of CN-AML)
- Exon 12 mutations leading to cytoplasmic shift of protein
- Immunophenotype
  
  *High CD33 expression (Low to absent CD34)*
  
- Potential impact of ATRA as molecular therapy
  
  *Not hypothesis-driven Empirical observation*

Phase III study of chemo +/- ATRA in younger AML patients - AMLSG 07-04

### All Patients

<table>
<thead>
<tr>
<th>Time (years)</th>
<th>Overall survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>1</td>
<td>75</td>
</tr>
<tr>
<td>2</td>
<td>50</td>
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<tr>
<td>3</td>
<td>25</td>
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<td>6</td>
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<tr>
<td>7</td>
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<td>8</td>
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</tbody>
</table>

ATRA, n=511

no ATRA, n=508

\( p = 0.09 \)

### ELN Favorable-Risk*

<table>
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<th>Time (years)</th>
<th>Overall survival (%)</th>
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<tbody>
<tr>
<td>0</td>
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<td>7</td>
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<tr>
<td>8</td>
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</tbody>
</table>

Favorable

ATRA

no ATRA

\( p = 0.02 \)

Other

ATRA

no ATRA

\( p = 0.19 \)

*inv(16), t(8;21), CEBPA\(^{dm}\), NPM\(^{mut}\)/FLT3-ITD\(^{neg}\)

Schlenk RF, et al. EHA 2014, abstract #S646.
**NPM1mut Acute Myeloid Leukemia**  
**AMLSG 09-09 (active)**

Phase III Study of Chemotherapy in Combination with ATRA with or without Gemtuzumab Ozogamicin (Mylotarg)

*ATRA*-ICE  
Consolidation 1  
Consolidation 2+3

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

- **Consolidation 1**  
  - ATRA Cytarabine*
  - ATRA Cytarabine*

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

---

*NPM1 Mutation Screening within 48 Hours*

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: R.F. Schlenk; Supported by Else Kröner-Fresenius-Foundation*
Survival in $NPM1^{\text{mut}}/FLT3-ITD^{\text{neg}}$ AML

AMLSG 09-09: trial vs. historical Control

Age 18-60 years

- AMLSG 09-09 $n=125$
- Historical control, $n=422$

Age $\geq 61$ years

- AMLSG 09-09 $n=104$
- Historical control, $n=118$

Schlenk RF, et al. AMLSG. Unpublished data.
Phase III Study of Chemotherapy + Midostaurin (PKC412) or Placebo in Newly Diagnosed Patients ≤ 60 Years of Age with FLT3 Mutated Acute Myeloid Leukemia (RATIFY)

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

Induction

- Daunorubicin Cytarabine + Placebo
- Daunorubicin Cytarabine + Midostaurin

Consolidation x4**

- High-Dose Cytarabine + Placebo
- High-Dose Cytarabine + Midostaurin

Maintenance

- Placebo
- Midostaurin

FLT3 mutation screening within 48 hours*

R

n=717; screened: 3,279 (May 2008 – Sept 2011)

* Patients may receive hydroxyurea during screening phase
** Patients with an HLA-compatible family donor may proceed to allogeneic HSCT
ClinicalTrials.gov NCT00651261
Phase III Study of Chemotherapy + Midostaurin (PKC412) or Placebo in Newly Diagnosed Patients ≤ 60 Years of Age with FLT3 Mutated Acute Myeloid Leukemia (RATIFY)

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

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


* controlled for FLT3 subtype (TKD, ITD-Low, ITD-High)
Overall Survival - Post-Transplant

Treatment with Midostaurin increases OS after HCT in CR1

HCT, hematopoietic cell transplantation
Phase II study of chemotherapy + midostaurin followed by allogeneic HCT and midostaurin maintenance in AML with FLT3-ITD (18-70 yrs) AMLSG 16-10 Trial

FLT3-mutation screening within 48 hours*

Dauno Cytarabine → High-Dose Cytarabine*

Midostaurin**

1st priority

Early Allogeneic HCT

1-yr maintenance
Start: 30 d after allo

Midostaurin

2nd priority

3x High-Dose Cytarabine

Midostaurin

1-yr maintenance

* Optional 1st consolidation before allo HSCT

**Midostaurin: start on day 8, thereafter continuous dosing

ClinicalTrials.gov Identifier: NCT01477606 (active since 2011)

Supported by Novartis
Relative selectivity and potency ($IC_{50}$) of TKIs against FLT3-ITD

- 1\textsuperscript{st} generation TKIs non-selective; unfavorable safety profile; when used as single agent, only transient blast reductions observed
- 2\textsuperscript{nd} generation TKIs (quizartinib [AC220], crenolanib, gilteritinib [ASP2215]) more selective and more potent

Phase III study of chemotherapy with or without crenolanib in relapsed / refractory AML with FLT3 mutations - AMLSG 19-13

Relapsed/refractory AML with FLT3 mutations

n=293, 1:1

Induction

Consolidation

Maintenance

MC + Placebo

MC# + Placebo

Allo HCT*

3x IDAC + Placebo

1-yr Placebo

MC + Crenolanib

MC# + Crenolanib

Allo HCT*

3x IDAC + Crenolanib

1-yr Crenolanib

# Optional second cycle of MC (mitoxantrone, intermediate-dose cytarabine)

* First priority for consolidation is allogeneic HCT

Supported by AROG Pharmaceuticals
Refined molecular diagnostics in AML

- Targeted resequencing of 111 myeloid cancer genes (combined with cytogenetic profiles) in 1540 AML
- 5236 driver mutations (i.e., fusion genes, copy number alterations, gene mutations) involving 77 loci
- 6 genes mutated in >10% pts; 13 genes 5-10% pts; 24 genes 2-5% pts; 37 genes <2% pts

Pairwise interactions: 300 AML

Current average study cohort size for any given tumor type
Pairwise interactions: 600 AML
Pairwise interactions: 900 AML
Pairwise interactions: 1200 AML
Pairwise interactions: 1500 AML
Gene-gene interactions redefine outcomes within class

CR, complete remission; RD, refractory disease; DiCR, death in CR; DaR, death after relapse; AaR, alive after relapse; AinCR, alive in CR
NGS-based routine AML diagnostics

Targeted Re-Sequencing in routine AML diagnostics

- e.g. with the aid of Illumina sequencing technology (MiSeq)
  => „Myeloid Panel“

Building up databases

=> Linking genetic and clinical information („Knowledge Databases“)

Continuous process
(data sets from older pts, targeted therapies, etc.)

Individualized risk prediction and therapeutic decision making
Prototype:

⇒ Individual risk prediction depending on different treatment options

49yr old male
NK
NPM1, DNMT3A, IDH1

Gerstung et al. Nat Genet 2017
Genetics guided AML therapy

**Genotype**

- APL [PML-RARA]
- CBF-AML [KIT]
- AML FLT3mut
- AML NPM1mut
- AML MLLrearr
- AML IDH1/2mut
- Other subtypes, mainly high-risk

**Trial**

- NAPOLEON GIMEMA/AMLSG/SAL
  - APOLLO +/- ATO-ATRA-Ida
- +/- Dasatinib AMLSG 21-13
- Midostaurin AMLSG 16-10
  - +/- Crenolanib AMLSG 19-13
- ATRA +/- GO AMLSG 09-09
- Palbociclib (CDK6) AMLSG 23-14
- AG-120/AG-221 AG-221-AML-005
- Vosaroxin AMLSG 24-15
- ABT-199, BGB324, …

Molecular Screening 24-48 hrs
Precision medicine in AML: fact or fiction?

• We have entered a new era in leukemia genomics
  ⇒ however, whole exome/genome sequencing remain research tools
• Currently, cytogenetics and NPM1, CEBPA, FLT3, RUNX1, ASXL1 and TP53 mutational screening are standard of care (ELN)
  ⇒ targeted gene panel testing
• Explosion of knowledge starts to be translated into therapeutic benefit
  ⇒ Building up large knowledge data bases
  ⇒ Number of novel compounds are at the horizon that hold promise to enter the clinic
• Major challenge: identification of predictive biomarkers that help selecting the appropriate therapy for an individual patient
  ⇒ integrate biosampling, companion studies
• Enter your patients, younger or older, on a clinical trial!