OSHO AML Studies

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Acute Myeloid Leukemia (AML) < 60 years: Different Treatment Strategies Versus a Common Standard Arm—Combined Prospective Analysis by the German AML Intergroup

CR > 70%; OS 41.4%-47.5%!!

Büchner T et al. JCO; 2012
Age < 60 years; de novo and secondary AML

**AML ’96**

- **Induction A**
  - CR
  - **Consol A**
    - CR
    - **Consol A**
      - HLA-identical sibling
        - **Consol A**
          - **Consol A**
            - PR, NR: off study
            - Option: auto-HCT (≤ 55 yrs.)

- **Induction B**
  - CR
  - **Consol A**
    - CR
    - **Consol A**
      - PR, NR: off study

**AML ’2002**

- **Induction 1**
  - CR
  - **Consol**
    - **Consol 2**
      - **Consol 3**

- **Induction 2a**
  - PR, NR
  - **Consol**
    - **Consol**
      - **Consol**
        - HCT as soon as possible

- **Induction 2b**
  - PR, NR
  - **Consol**
    - **Consol 2**
      - **Consol 3**

**Standard arm**
Survival in patients with AML < 60 years according to cytogenetics

- **CBF**
  - AML ’96, n=249
  - AML ’02, n=440
  - \( p = 0.9 \)

- **Others**
  - \( p = 0.15 \)

- **NC**
  - \( p = 0.8 \)

- **High risk**
  - \( p < 0.0005 \)
Allogeneic HCT in intermediate risk AML in CR1


Metaanalysis
5 prospective Studies:
MRD: n = 1151
„donor vs. no donor“ / „intention to treat“
Survival benefit for allo HCT trend


Metaanalyse
6 prospective Studies:
„donor vs. no donor“ (n=603 vs. 1106)
Significant survival benefit for allo HCT
Survival in patients with AML < 60 years according to cytogenetics

- **CBF**
  - \( p = 0.9 \)

- **Others**
  - \( p = 0.15 \)

- **NC**
  - \( p = 0.8 \)

- **High risk**
  - \( p < 0.0005 \)

Allogeneic HCT
Treatment strategies in patients with AML < 60 years

**Cytogenetics**

- **Favorable-risk**
  - Consol
  - MRD monitoring

- **Intermediate risk**
  - Mito-FLAG
  - ID-AraC/Mito

- **High risk**
  - ID-AraC/IDA

**Upfront registration**

- CR1/CR1i & HLA-identical donor
- allo HCT
- auto Tx

**ETAL-1 (SAL, AMLCG, OSHO)**

- Konsol 1
- Konsol 2
- Konsol 3
- allo HCT
- auto Tx

*For OSHO centers not taking part in the ETAL study*
AML studies in patients > 60 years

AML > 60

kurativ (75,5%)

Intergroup AML 2004

AML 2004 (OSHO #69)

OSHO/EBMT

palliativ (19,0%)

*Azacitidine OSHO #75

*Closed

supportiv (5,5%)

*Clofarabine OSHO #75

RAS-AZIC OSHO #83
AML studies in patients > 60 years

**AML > 60**

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**OSHO/EBMT**

**RAS-AZIC OSHO #83**

*Closed*
Factors Influencing CR Rate in elderly AML
Report From the German Intergroup Study

median follow up of patients alive:
Group B (38 mts)
Group A (23 mts)
Common arm (34 mts)
Factors Influencing CR Rate in elderly AML

Conclusions

➢ High CR rates can be achieved in patients with AML >60 years
➢ CR-rate depends on:
  ➢ Age
  ➢ WBC count
  ➢ AML type
  ➢ cytogenetic risk

➢ OS  Cytogenetics, age, diagnosis, WBC count, gender
➢ RFS  Cytogenetics, age

➢ No difference between common arm vs. Group A and B arms in OS, RFS, EFS

Niederwieser D et al. ASH 2012; Abstract 128
Intensive chemotherapy (IC) in patients with AML > 60 years and who are ‘fit´ for IC

n=1154

CR rate 61%
median OS 343 days
OS at 2 years 33%
OS at 5 years 18%

Study | CR rate | median OS | n
---|---|---|---
AML 93 | 61% | 343 days | 83
AML 97 | 61% | 343 days | 411
AML 04 | 61% | 343 days | 594
AML 04 IG | 61% | 343 days | 66
# Consolidation

## AML '97: DA 2 + 5

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose 1</th>
<th>Dose 2</th>
<th>Administration</th>
<th>Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mitoxantron</td>
<td>10 mg/m²</td>
<td>120 mg/m²</td>
<td>30 min Infusion</td>
<td>d 1 + 2</td>
</tr>
<tr>
<td>Ara-C</td>
<td>120 mg/m²</td>
<td></td>
<td>12stdl. als 1h-Infusion</td>
<td>d 1 - 5</td>
</tr>
</tbody>
</table>

## AML 2004 (OSHO #69) IMD-Ara-C / Mito

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose 1</th>
<th>Dose 2</th>
<th>Administration</th>
<th>Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mitoxantron</td>
<td>10 mg/m²</td>
<td>0.5 g/m²</td>
<td>30 min Infusion</td>
<td>d 1 + 2</td>
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<tr>
<td>Ara-C</td>
<td></td>
<td></td>
<td>12stdl. als 3h-Infusion</td>
<td>d 1 + 3 + 5</td>
</tr>
<tr>
<td>Pegfilgrastim</td>
<td>6 mg</td>
<td></td>
<td>1x s.c.</td>
<td>d 8</td>
</tr>
</tbody>
</table>
DA $2+5$ vs. IMD-Ara-C/Mito

AML 97 $n = 126$

AML 2004 $n = 145$

$RFS$

Years after CR

$p = .99$

$p = .84$

Survival

Years after CR

$p = .17$

$p = .04$
AML 2004: Landmark-Analysis CT vs. HCT

\[ p = 0.006 \]

\[ p = 0.4 \]
AML studies in patients > 60 years

AML > 60

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Intergroup AML 2004

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*Azacitidine
OSHO #75

supportiv (5,5%)

*Clofarabine
OSHO #75

AML 2004 (OSHO #69)

*Closed

RAS-AZIC OSHO #83

OSHO/EBMT
EBMT study in AML patients older than 60 years in first CR

**Randomized, phase 3 study**

Conventional chemotherapy vs low-dose total body irradiation-based conditioning and HSCT (related and unrelated donors) as consolidation therapy

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**EBMT, HOVON, OSHO, ALFA, CETLAM, GOELAMS, SAKK, EORTC**

EMEA EudraCT number 2007-003514-34.

AML studies in patients > 60 years

AML > 60

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AML 2004 (OSHO #69)

OSHO/EBMT

RAS-AZIC OSHO #83
AML studies in patients > 60 years

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- Supportīv (5,5%)

AML 2004 (OSHO #69)

OSHO/EBMT

RAS-AZIC OSHO #83

*Closed
Azacitidine in AML patients not eligible for or resistant to chemotherapy

Median OS for patients with stable disease (SD) was 4 months, whereas median OS for patients with CR, PR, or HI was not reached ($p = 0.045$)

**OS in patients with newly diagnosed or relapsed/refractory AML**

- Newly diagnosed (n = 20)
- Relapsed or refractory (n = 20)

**OS according to haematological response**

- NE (n = 11)
- CR + PR + HI (n = 12)
- SD (n = 15)
- PD (n = 2)

Azacitidine in AML patients not eligible for or resistant to chemotherapy

Bone marrow blasts on day 15 of cycle 1 and not early blast clearance correlated with subsequent response

\( P = 0.006 \)

**Trial Design – Phase II**

1. **Induction Chemotherapy**
   - **Day 15**
     - Blasts ≥ 45%
     - Aza 75mg/m² 5 or 7 days
   - d 17-45
   - Blasts <
   - **Day 56**
     - CR, CRi
     - Aza 75mg/m² 5 or 7 days
   - d 58-86
   - Not CR, CRi

2. **Induction Chemotherapy**
   - d 56 – 62, d 84, ...

**Aza-Maintenance Therapy**
(Start every 4 weeks)

- Aza Maintenance, until:
  - HCT
  - Relapse
  - PD

- **Follow-up:** up to 2 years after start of trial treatment

**Bone marrow blasts (%)**

- CR/PR
- SD

**Day 15**
- p=0.006

**“RAS-AZIC”**

**OSHO #083**
Aza Maintenance Therapy (Start every 4 weeks)

Day 90
Aza 75mg/m2
5 or 7 days

1. Induction Chemotherapy

Day 15
Blasts < 45%
Day 17 - 45

Blasts ≥ 45%
Day 28 - 32/34

Aza 75mg/m2
5 or 7 days

2. Induction Chemotherapy

Day 56
CR, CRi
Not CR, CRi

Day 58 - 86
Not PR, CR, CRi
→ End of trial treatment

Aza-Maintenance Therapy (Start every 4 weeks)

Day 90
PR, CR, CRi

HCT
Relapse
PD

Follow-up: up to 2 years after start of trial treatment

Trial Design – Phase II

Central laboratory assessment

Follow-up: up to 2 years after start of trial treatment

“RAS-AZIC”

OSHO #083
RAS-AZIC

Phase I

Doselevel 1

Aza 75mg/m²
5 days


d 1-5

d 17- 45

Induction Chemotherapy

Day 56

DLT 5 days ≤ 0/3 or 1/6

Phase II with Aza 75mg/m² 5 days

DLT 5 days >1/6

Phase II with Aza 75mg/m² 7 days

Doselevel 2

Aza 75mg/m²
7 days


d 1-7

d 17- 45

Induction Chemotherapy

Day 56

DLT 7 days >1/6

DLT 7 days ≤ 0/3 or 1/6

: Full Safety Evaluation
Vielen Dank