„Treatment of Acute Myeloid Leukemia: Present Status and New Directions III“

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• Experience
• AML Biology
• Older Age AML
• Novel Approaches
• Cooperation
Complete remissions (CR) and 4-5-year continuous complete remissions (CCR) in multicenter randomized trials in the order of patients age:

**Younger patients**

<table>
<thead>
<tr>
<th>Publication</th>
<th>Age</th>
<th>No. of Patients</th>
<th>% CR</th>
<th>% CCR at 4-5 Y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hann et al. 1997</td>
<td>0-55</td>
<td>1857</td>
<td>82</td>
<td>42</td>
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<tr>
<td>Burnett et al. 1998</td>
<td></td>
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<tr>
<td>Mandelli et al. 1992</td>
<td>15-55</td>
<td>448</td>
<td>68</td>
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<tr>
<td>Cassileth et al. 1998</td>
<td>16-55</td>
<td>740</td>
<td>70</td>
<td>35-43</td>
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<tr>
<td>Rai et al. 1981</td>
<td>0-60</td>
<td>247</td>
<td>36-59</td>
<td>22 (not age specific)</td>
</tr>
<tr>
<td>Yates et al. 1982</td>
<td>1-60</td>
<td>427</td>
<td>57-72</td>
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<td>Büchner et al. 1985</td>
<td>16-60</td>
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<td>Rees et al. 1986</td>
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<td>Hayat et al. 1986</td>
<td>10-60</td>
<td>257</td>
<td>66</td>
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<tr>
<td>Zitoun et al. 1995</td>
<td>11-59</td>
<td>941</td>
<td>66</td>
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<tr>
<td>Preisler et al. 1987</td>
<td>14-60</td>
<td>564</td>
<td>65</td>
<td>17</td>
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<td>Hansen et al. 1991</td>
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<td>60</td>
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<tr>
<td>Dillman et al. 1991</td>
<td>15-60</td>
<td>226</td>
<td>69</td>
<td>10 (not age specific)</td>
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<tr>
<td>Cassileth et al. 1992</td>
<td>15-60</td>
<td>376</td>
<td>71</td>
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<tr>
<td>Mayer et al. 1994</td>
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<td>Bishop et al. 1996</td>
<td>15-60</td>
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<td>Weick et al. 1996</td>
<td>&lt; 65</td>
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<td>Büchner et al. 1999</td>
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</tbody>
</table>
Complete remissions (CR) and 4-5-year continuous complete remissions (CCR) in multicenter randomized trials in the order of patients age:

**Older patients**

<table>
<thead>
<tr>
<th>Publication</th>
<th>Age</th>
<th>No. of Patients</th>
<th>% CR</th>
<th>% CCR at 4-5 Y</th>
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<tr>
<td>Löwenberg et al. 2003</td>
<td>18-60</td>
<td>640</td>
<td>81</td>
<td>39</td>
</tr>
<tr>
<td>Hayat et al. 1986</td>
<td>60-65</td>
<td>30</td>
<td>47</td>
<td>no age specific data</td>
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<tr>
<td>Hansen et al. 1991</td>
<td>60-65</td>
<td>39</td>
<td>46</td>
<td>30</td>
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<tr>
<td>Cassileth et al. 1992</td>
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<td>52</td>
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<td>Rowe et al. 1995</td>
<td>55-70</td>
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<td>61</td>
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<tr>
<td>Witz et al. 1998</td>
<td>55-75</td>
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<td>62</td>
<td>23</td>
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<tr>
<td>Goldstone et al. 2001</td>
<td>56-80</td>
<td>1311</td>
<td>50-62</td>
<td>15-18</td>
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<tr>
<td>Anderson et al. 2002</td>
<td>56-84</td>
<td>328</td>
<td>38</td>
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<tr>
<td>Rai et al. 1981</td>
<td>60+</td>
<td>105</td>
<td>16-45</td>
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</tr>
<tr>
<td>Yates et al. 1982</td>
<td>60-84</td>
<td>226</td>
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<td>Büchner et al. 1985</td>
<td>60-78</td>
<td>79</td>
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<td>0-28</td>
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<td>Büchner et al. 2003</td>
<td>60-82</td>
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<td>60</td>
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<td>Rees et al. 1986</td>
<td>60-83</td>
<td>305</td>
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<tr>
<td>Preisler et al. 1987</td>
<td>60+</td>
<td>104</td>
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<td>Dillman et al. 1991</td>
<td>60-83</td>
<td>100</td>
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<tr>
<td>Mayer et al. 1994</td>
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<tr>
<td>Stone et al. 1995</td>
<td>60+</td>
<td>388</td>
<td>53</td>
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<tr>
<td>Büchner et al. 1997</td>
<td>60+</td>
<td>340</td>
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<td>Dombret et al. 1995</td>
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<td>Löwenberg et al. 1998</td>
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<td>Büchner et al. 2006</td>
<td>60-85</td>
<td>930</td>
<td>53</td>
<td>16</td>
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</table>
Mean percent complete remissions in 31 randomized multicenter trials and 19,882 patients

<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td></td>
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</tr>
<tr>
<td>&lt; 60</td>
<td>66 %</td>
<td>72 %</td>
</tr>
<tr>
<td>60+</td>
<td>42 %</td>
<td>51 %</td>
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</table>

Publication: ctt-journal 2008;1:7-17
### Mean percent continuous complete remissions at 4-5 years in 31 randomized multicenter trials

<table>
<thead>
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<th></th>
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<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 60</td>
<td>17%</td>
<td>34%</td>
</tr>
<tr>
<td>60+</td>
<td>11%</td>
<td>15%</td>
</tr>
</tbody>
</table>

*Publication Year: ctt-journal 2008;1:7-17*
AMLCG 81: All Ages

- Maintenance  N = 79
- No Maintenance  N = 82

Percent Relapse Free Survival

Years from CR

P = .00004
Maintenance : N = 197
S-HAM : N = 200

P = .023
• Experience

• AML Biology

• Older Age AML

• Novel Approaches

• Cooperation
AMLCG 92 + 99

Survival rates for different cytogenetic groups in AMLCG 92 and 99 trials. The graph shows the percentage of patients surviving different years from the start of therapy for favorable, intermediate, normal, unfavorable, and complex karyotypes.

Schoch C et al., Haferlach C et al.
Patients with Normal Cytogenetics in AMLCG 99

<table>
<thead>
<tr>
<th>Cytogenetic Status</th>
<th>N</th>
<th>Censored</th>
</tr>
</thead>
<tbody>
<tr>
<td>NPM1+/FLT3-</td>
<td>264</td>
<td>164</td>
</tr>
<tr>
<td>NPM1+/FLT3+</td>
<td>180</td>
<td>70</td>
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<tr>
<td>NPM1-/FLT3-</td>
<td>371</td>
<td>134</td>
</tr>
<tr>
<td>NPM1-/FLT3+</td>
<td>76</td>
<td>21</td>
</tr>
</tbody>
</table>

Years from Start of Therapy

Percent Survival

0 25 50 75 100
• Experience
• AML Biology
• Older Age AML
• Novel Approaches
• Cooperation
AMLCG 99: All Patients (N=2734)

Percent Survival

Years from Start of Therapy

<60 Y: N=1262 (Censored 599)
60+ Y: N=1472 (Censored 357)
CR Patients

Cumulative Incidence of Relapse (%)

- < 60 Y N = 798
- 60+ Y N = 735

P < 0.0001

Years from CR
Raisa Gorbacheva Memorial Meeting
"Treatment of Acute Myeloid Leukemia: Present Status and New Directions III"

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Creutzig et al. Cancer 2007

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20.09.2009
# 19
Patients with CBF Leukemia

- < 60 Years: N = 143 (Censored 103)
- 60+ Years: N = 55 (Censored 22)

P < .0001
CR Patients with CBF Leukemia

Cumulative Incidence of Relapse (%)

Years from CR

< 60 Y N = 108

60+ Y N = 38

P = .0006

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Patients with Normal Cytogenetics and NPM1mut/FLT3-ITDneg

<table>
<thead>
<tr>
<th>Years from Start of Therapy</th>
<th>Percent Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 60 Years: N = 141</td>
<td>(Censored 107)</td>
</tr>
<tr>
<td>60+ Years: N = 123</td>
<td>(Censored 57)</td>
</tr>
</tbody>
</table>

P < .0001
CR Patients with Normal Cytogenetics and NPM1mut/FLT3-ITDneg

Cumulative Incidence of Relapse (%)

Years from CR

- < 60 Y: N = 114
- 60+ Y: N = 92

P < .0001
Cytogenetic Groups

Age 60+

Mutations

NPM1/FLT3

Age < 60

ABNORMAL CYTOGENETICS

NORMAL CYTOGENETICS

favorable
intermediate
unfavorable

19%
13%
12%
10%
9%
7%
9%
17%
19%
6%
8%

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Principle of ChIP-Chip

1. Crosslink proteins to chromatin in living cells
2. Lyse cells and fragment chromatin by sonication
3. Immunoprecipitate protein of interest: acetylated or methylated Histone
4. Reverse crosslinks and purify DNA
5. Amplify and label DNA
6. Hybridization

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Müller-Tidow C, 2008

20.09.2009
# 25
• Experience

• AML Biology

• Older Age AML

• Novel Approaches

• Cooperation
# Novel Approaches in AML

<table>
<thead>
<tr>
<th>Targets</th>
<th>Approach</th>
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<tbody>
<tr>
<td>GvL target</td>
<td>Allo SCT (MRD, MUD)</td>
</tr>
<tr>
<td>RARA</td>
<td>ATRA</td>
</tr>
<tr>
<td>PML</td>
<td>Arsenic trioxide</td>
</tr>
<tr>
<td>BCR/ABL, c-kit</td>
<td>Imatinib, Dasatinib, Nilotinib</td>
</tr>
<tr>
<td>FLT3 (wild type and mutated)</td>
<td>Sorafenib, Midostaurin</td>
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<tr>
<td>Tyrosin Kinase</td>
<td>SU5416</td>
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<tr>
<td>Farnesyl-Transferase</td>
<td>Tipifarnib</td>
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<tr>
<td>DNA synthesis</td>
<td>Clofarabine</td>
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<td>Histone deacetylation (HDAC)</td>
<td>Valproic acid</td>
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<tr>
<td>Hypermethylation (DNMT)</td>
<td>5-azacytidine, Decitabine</td>
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<tr>
<td>CD33</td>
<td>GO (Mylotarg)</td>
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</table>
Course 1

ADE 10+3+5 ± Mylotarg

DA 3+10 ± Mylotarg

FLAG-Ida ± Mylotarg

Risk group assessment of status. If **poor risk**, **OPTIONAL** to continue in AML15 or to enter an NCRI high risk trial if available

Course 2

ADE 8+3+5

DA 3+8

FLAG-Ida

Course 3

MACE ± Mylotarg

Ara-C 1.5g/m² ± Mylotarg

Ara-C 3g/m² ± Mylotarg

Standard/poor risk adults

Poor risk children

Donor available, suitable for Allo SCT

Course 4

MidAC

Ara-C 1.5g/m²

Ara-C 3g/m²

Course 5

No further treatment

Ara-C 1.5g/m²

Randomise

Elect

From A. Burnett 2007
To compare three induction schedules (namely ADE, DA and FLAG-Ida)

Course 1
- ADE 10+3+5 ± Mylotarg
- DA 3+10 ± Mylotarg
- FLAG-Ida ± Mylotarg

Course 2
- DA 3+8
- FLAG-Ida

Risk group assessment of status. If poor risk, OPTIONAL to continue in AML15 or to enter an NCRI high risk trial if available.

Course 3
- Ara-C 3g/m² ± Mylotarg
- Ara-C 1.5g/m²
- MidAC

Course 4
- Ara-C 1.5g/m² ± Mylotarg
- Ara-C 3g/m²
- Standard Allo SCT

Course 5
- No further treatment
- Ara-C 1.5g/m²

From A. Burnett 2007
To compare three induction schedules (namely ADE, DA and FLAG-Ida)

To assess the value of Mylotarg during induction when used in combination with ADE or DA or FLAG-Ida

From A. Burnett 2007
AML 15: Overall Survival

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20.09.2009 # 32
AML CG 99
All Patients < 60 Years with Complex Karyotypic Abnormalities

Update 5/2006

RD : N = 18 (Censored 7)
URD : N = 21 (Censored 10)
No Tx : N = 63 (Censored 7)

Percent Survival

Years from Start of Therapy

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20.09.2009
# 33
Related versus Unrelated Donors: Overall Survival

AML: TBI 8 Gy / F 120 ± ATG

CR1/CR2 4 yr: 83% (95% CI: 70 - 96)

non-CR 4 yr: 16% (95% CI: 3 - 29)

• Experience
• AML Biology
• Older Age AML
• Novel Approaches
• Cooperation
Overall Survival

Months after start of induction therapy

Probability

2784 Patients

0 6 12 18 24 30 36 42 48 54 60 66 72

0.0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.0

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20.09.2009
# 38
Probability of relapse-free survival

Months after CR in induction therapy

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20.09.2009
# 39
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Raisa Gorbacheva Memorial Meeting
„Treatment of Acute Myeloid Leukemia: Present Status and New Directions III“

20.09.2009

# 40
AML-BFM Studies 78-93 - event free survival -
AML-BFM 98 Intent-to-treat analysis overall survival

No donor (N=188, 77 events)
HLA-id. donor (N=58, 20 events)

Log-Rank p = .16

.56, SE=.04
.58, SE=.09

0.0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.0
0 1 2 3 4 5 6 7 8 years

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20.09.2009
# 44
CTSG ETAL-1 Trial

Trial cohort

Mrel/unrelID (≥ 7/8)

Off study

Blast clearance incomplete

Induction therapy

CR1

R

Evaluation in CR: Strata allocation

Early AlloHSCT

Salvage AlloHSCT
Raisa Gorbacheva Memorial Meeting
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1999