“Allogeneic Stem Cell Transplantation for Acute Leukemia ”

Prof. Mohamad Mohty, M.D., Ph.D.

Hopital Saint-Antoine,
INSERM UMR 938
Paris, France
AML is a heterogeneous disease

2008 WHO classification

Acute myeloid leukemia with recurrent genetic abnormalities
- AML with t(8;21)(q22;q22); RUNX1-RUNX1T1
- AML with inv(16)(p13.1q22) or t((16;16)(p13.1;q22); CBFB-MYH11
- APL with t(15;17)(q22;q12); PML-RARA
- AML with t(9;11)(p22;q23); MLLT3-MLL
- AML with t(6;9)(p23;q34); DEK-NUP214
- AML with inv(3)(q21q26.2) or t(3;3)(q21;q26.2); RPN1-EVI1
- AML (megakaryoblastic) with t(1;22)(p13;q13); RBM15-MKL1
- Provisional entity: AML with mutated NPM1
- Provisional entity: AML with mutated CEBPA

Acute myeloid leukemia with myelodysplasia-related changes

Therapy-related myeloid neoplasms

Acute myeloid leukemia, not otherwise specified
- AML with minimal differentiation
- AML without maturation
- AML with maturation
- Acute myelomonocytic leukemia
- Acute monoblastic/monocytic leukemia
- Acute erythroid leukemia
  - Pure erythroid leukemia
  - Erythroleukemia, erythroid/myeloid
- Acute megakaryoblastic leukemia
- Acute basophilic leukemia
- Acute panmyelosis with myelofibrosis

Myeloid Sarcoma

Myeloid Proliferations related to Down Syndrome
- Transient abnormal myelopoiesis
- Myeloid leukemia associated with Down syndrome

Blastic Plasmacytoid Dendritic Cell Neoplasm
Simplified Classification of AML

- AML sensitive to conventional chemotherapy
  - CBF leukemias (without c-KIT mutation)
  - Diploid AML with NPM1 and CEBPα mutation (without FLT3 mutation)
  - Dose intensification of chemotherapy may be helpful

- Chemo-resistant and high risk AML
  - New agents are needed
  - Allo-SCT in the mainstay of therapy
AML: Change in overall survival with time

(A) Age 15 to 59 years

(B) 60 or more years
Therapy for AML (non-APL): Decision checkpoints and Factors influencing therapeutic decisions

- Diagnosis
  - Intensive CT
    - Postremission therapy
      - Relapse
        - Rescue treatment
  - Performance status
  - Comorbidities
  - Pharmacogenetics
  - Cytogenetics
  - Molecular profile
  - MRD persistence

Factors influencing therapeutic decisions:
- Age
- Performance status
- Comorbidities
- Pharmacogenetics
- Cytogenetics
- Molecular profile
- MRD persistence
Patients in 1st CR:

- Repetitive HDAC benefit CBF AML (probably, also NPM1+/FLT3-ITD-)
- The number of consolidation courses in intermediate-risk AML is unclear.
- Additional drugs do not seem to improve the results of cytarabine alone. Investigational: GO, ATRA, FLT3 inhibitors?
- Repetitive courses do not favor AML with adverse cytogenetics profile
## Allogeneic Stem Cell Transplantation for Acute Myeloid Leukemia in First Complete Remission

Systematic Review and Meta-analysis of Prospective Clinical Trials

### Figure 2. Relapse-Free Survival (RFS) Benefit of Allogeneic SCT for AML in First Complete Remission

<table>
<thead>
<tr>
<th>Source</th>
<th>No. of Patients</th>
<th>No. of Trials</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferrant et al, 1991</td>
<td>24</td>
<td></td>
<td>0.50 (0.30-0.85)</td>
</tr>
<tr>
<td>Cassileth et al, 1992</td>
<td>54</td>
<td></td>
<td>0.84 (0.48-1.49)</td>
</tr>
<tr>
<td>Schiller et al, 1992</td>
<td>28</td>
<td>54</td>
<td>0.88 (0.48-1.64)</td>
</tr>
<tr>
<td>Archimbaud et al, 1994</td>
<td>27</td>
<td>31</td>
<td>0.69 (0.36-1.32)</td>
</tr>
<tr>
<td>Hewlett et al, 1995</td>
<td>53</td>
<td>110</td>
<td>0.85 (0.58-1.27)</td>
</tr>
<tr>
<td>Sierra et al, 1996</td>
<td>47</td>
<td>68</td>
<td>1.56 (0.95-2.57)</td>
</tr>
<tr>
<td>Haroussean et al, 1997</td>
<td>88</td>
<td>134</td>
<td>0.94 (0.67-1.33)</td>
</tr>
<tr>
<td>Keating et al, 1998</td>
<td>279</td>
<td>355</td>
<td>0.77 (0.63-0.94)</td>
</tr>
<tr>
<td>Sovak et al, 2000</td>
<td>89</td>
<td>174</td>
<td>0.83 (0.58-1.19)</td>
</tr>
<tr>
<td>Suciu et al, 2003</td>
<td>293</td>
<td>441</td>
<td>0.80 (0.64-1.00)</td>
</tr>
<tr>
<td>Jourdan et al, 2005</td>
<td>182</td>
<td>290</td>
<td>0.75 (0.59-0.96)</td>
</tr>
<tr>
<td>Burnett et al, 2006</td>
<td>419</td>
<td>868</td>
<td>0.81 (0.70-0.95)</td>
</tr>
<tr>
<td>Cornelissen et al, 2007</td>
<td>326</td>
<td>599</td>
<td>0.77 (0.64-0.91)</td>
</tr>
</tbody>
</table>
Even patients with a normal karyotype are diverse

Döhner H et al, Blood 2010
Sequencing the entire coding regions of TET2, ASXL1, DNMT3A, CEBPA, PHF6, WT1, TP53, EZH2, RUNX1, PTEN FLT3, NPM1, HRAS, KRAS, NRAS, KIT, IDH1, and IDH2

## Targeted agents under investigation in AML

<table>
<thead>
<tr>
<th>Class</th>
<th>Agent</th>
<th>Trial status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Farnesyl transferase inhibitors</td>
<td>Tipifarnib</td>
<td>Phase II/III</td>
</tr>
<tr>
<td>FLT3 inhibitors</td>
<td>Lestaurtinib, Midostaurin, Sorafenib, AC220</td>
<td>Phase II/III</td>
</tr>
<tr>
<td>Polo-like kinase inhibitors</td>
<td>Volasertib</td>
<td>Phase II/III</td>
</tr>
<tr>
<td>Aminopeptidase inhibitors</td>
<td>Tosedostat</td>
<td>Phase I/II</td>
</tr>
<tr>
<td>Topoisomerase II inhibitors</td>
<td>Voreloxin</td>
<td>Phase II/III</td>
</tr>
<tr>
<td>NF-kB inhibitors</td>
<td>Bortezomib</td>
<td>Phase I/II</td>
</tr>
<tr>
<td>PI3K/AKT/mTOR inh</td>
<td>Rapalogs, BKM120</td>
<td>Phase I/II</td>
</tr>
<tr>
<td>Hsp90 inhibitors</td>
<td>Ganetespib</td>
<td>Phase I/II</td>
</tr>
<tr>
<td>Hedgehog inhibitors</td>
<td>PF-04449913</td>
<td>Phase I/II</td>
</tr>
</tbody>
</table>
**FLT3 mutations**

- ~25% of patients with AML
- High incidence in AML with
  - *NPM1* mutations (40%)
  - t(15;17)(q21;q21)/*PML-RARA* (40-45%)
  - t(6;9)(p23;q34)/*DEK-NUP214* (75%)
- Associated with inferior prognosis:
  - Allelic ratio (mut/wt)
  - ITD insertion site

*FMS*-like tyrosine kinase 3

Fractionated Doses of Gemtuzumab Ozogamicin Combined to Standard Chemotherapy In Newly-Diagnosed de novo AML Patients Aged 50-70 Yrs

Randomization

Arm A
- DNR 60 mg/m² D1 to D3
- AraC 200 mg/m² D1 to D7

Arm B
- DNR 60 mg/m² D1 to D3
- AraC 200 mg/m² D1 to D7
- GO 3 mg/m² D1, D4, D7

2nd course if BM blasts >10% at D15
- DNR 60 mg/m² D1, D2
- AraC 1g/m²/12h D1 to D3

CR or CRp

1st CONSOLIDATION
- DNR 60 mg/m² D1
- AraC 1g/m²/12h D1 to D4
- GO 3 mg/m² D1

2nd CONSOLIDATION
- DNR 60 mg/m² D1, D2
- AraC 1g/m²/12h D1 to D4
- GO 3mg/m² D1

Castaigne et al., Lancet 2012
Overall survival

<table>
<thead>
<tr>
<th></th>
<th>A (control) (n=139)</th>
<th>B (GO) (n=139)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deaths</td>
<td>71</td>
<td>59</td>
</tr>
<tr>
<td>Median</td>
<td>19.2 mo</td>
<td>34 mo</td>
</tr>
<tr>
<td>2-year</td>
<td>43.5%</td>
<td>53.1%</td>
</tr>
<tr>
<td>HR</td>
<td>1</td>
<td>0.70 (95% CI)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(0.50-0.99)</td>
</tr>
</tbody>
</table>

P = 0.046
by the log-rank test

Castaigne et al., Lancet 2012
Azacitidine in AML

- 358 pts AZA-001; 113 ≥20% blasts (WHO AML)
- 55 randomized to AZA, 58 to CCR
- Median age 70 y.; poor cytogen 24%
- Median FU 20 m.; median cycles 8 (1-39)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>AZA</th>
<th>CCR</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Median OS (m)</td>
<td>24</td>
<td>16</td>
<td>.004</td>
</tr>
<tr>
<td>- % 2-yr survival</td>
<td>50</td>
<td>16</td>
<td>.004</td>
</tr>
<tr>
<td>- % CR</td>
<td>18</td>
<td>16</td>
<td>NS</td>
</tr>
</tbody>
</table>

- Survival better in int cytogen., not in unfavourable cytogenetics.

Fenaux et al. J Clin Oncol 2010
Randomized trial of Decitabine vs. treatment of choice in AML ≥ 65 years


CR/CRp
Decitabine 17.8%
TC 7.8%
P = .001
RIC allo-SCT: rationale

As a possible less toxic alternative to standard myeloablative allo-SCT, the use of RIC allo-SCT aims to:

*Shift the burden tumor eradication From Chemo-radiotherapy to Donor immune Cells*
RIC allo-SCT for AML: is it really worthwhile?
RIC allo-SCT for AML: “donor” vs. “no donor” (N=95; Intention-to-treat analysis)

Median FU = 60 months

In the multivariate analysis, only actual performance of RIC-allo-SCT (P=0.0005; RR=4.1; 95%CI, 1.8-9.1), was significantly predictive of an improved long term LFS
### Study: Standard vs RIC allo-SCT in AML-CR1: a prospective randomised study

<table>
<thead>
<tr>
<th>Study</th>
<th>outcome estimates at 36 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm</td>
<td>TRM</td>
</tr>
<tr>
<td>MA (n=90)</td>
<td>18%*</td>
</tr>
<tr>
<td>RIC (n=94)</td>
<td>11%*</td>
</tr>
</tbody>
</table>

*P-value TRM: 0.01

**Bornhauser et al. Lancet Oncol 2012**
Standard vs RIC allo-SCT in AML-CR1: a prospective randomised study

NRM: 18-40 years

NRM: 41-60 years

Incidences of relapse at 3 years were not different between both treatment arms.

Bornhauser et al. Lancet Oncol 2012
Impact of cytogenetics risk on outcome after RIC allo-SCT from an HLA identical sibling for AML in CR1 (N=378)

Median follow-up: 24 months (range, 1-93)

Leukemia-free survival

Good risk (n=21)
64 ± 11%

Intermediate risk (n=304)
57 ± 3%

Poor risk (n=53)
38 ± 7%

P=0.003

Years after allo-SCT

Chevallier et al. Bone Marrow Transplant 2012

The European Group for Blood and Marrow Transplantation
How to better select AML patients prior to RIC allo-SCT?
Whom to transplant in May 2014?
Favorable disease-risk AML: Allo-SCT in first CR

• Not indicated in first CR
Intermediate disease-risk AML: allo-SCT in first CR?

• Intermediate-risk cytogenetics (including normal) **without** favorable/unfavourable molecular profile and non-high MRD

• Consider transplant factors! (EBMT risk score, comorbidities: Autologous SCT? RIC even in non-old pts?)

Adverse disease-risk (cytogenetics/molecular profile/high MRD)

- Mandatory allogeneic transplantation (and Sib/URD/UCB search/haplo ASAP !)
Conclusions

- AML therapy remains non-specific and challenging for most patients.
- A number of demographic features can predict the outcome of treatment including cytogenetics and an increasing list of molecular features (ie, FLT3, NPM1, MLL, WT1, CEBPalpha, EVI1) ➔ multi-agent approach needed.
- Emerging therapies are promising, and targeted therapies started addressing small subgroups, **BUT allo-SCT will remain the recommended treatment for many patients**!
- RTC allo-SCT appears increasingly to be a safer procedure in the “older” AML patients.
- Prevention of relapse is mandatory.
"ALLOGENEIC STEM CELL TRANSPLANTATION FOR HIGH RISK MDS"
## MDS: Treatment Objectives

<table>
<thead>
<tr>
<th>IPSS</th>
<th>Objective</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk</td>
<td></td>
</tr>
<tr>
<td>Low Int-1</td>
<td>• Improve hematological parameters</td>
</tr>
<tr>
<td>High risk</td>
<td></td>
</tr>
<tr>
<td>Int-2 High</td>
<td>• Modify the natural history of the disease</td>
</tr>
</tbody>
</table>
RESULTS OF ALLO-SCT in MDS: LIMITING FACTORS

• No randomized trials

• No prospective evaluation of the role of chemotherapy

• Heterogeneous series
  – Age
  – Diseases (AML, MDS)

• Changes over time:
  – Classifications
    • FAB/WHO
    • IPSS
  – Supportive care
  – Novel therapies (5-Azacytidine, …)
In summary:

- Median Age = 35 y.
- 29 - 56 % DFS
- 16 - 48 % Relapse incidence
- 28 - 50 % TRM
How to Improve results of allo-SCT in MDS?

**TWO issues**

- Reduce morbidity and TRM (improvement of supportive care, e.g. new antifungal and antiviral drugs, growth factors etc. AND better donor selection AND introduction of RIC regimens)

- Reduce risk of relapse (prior and post-transplant strategies)
RIC allo-SCT for MDS

- **Median age:** 55 y.
- DFS: 30 to 86%
- Heterogeneous diseases
- Different types of donors
- Reproducibility?
- Multiple small series
- Short follow-up
In this analysis, disease stage at time of transplantation, but not recipient age or the intensity of the conditioning regimens, was the most important factor influencing outcomes (Lim et al. JCO 2010)
Prognostic factors for outcome after allo-SCT

- Marrow fibrosis  (Della Porta et al. J Clin Oncol 2008)
- Transfusion dependence  (Platzbecker et al. BBMT, 2008)
- Disease status: % of blasts AND Response to prior therapy
- ASBMT has identified pre-transplant cytoreductive therapy as a critical area for investigation!  (Oliansky DM et al., BBMT 2009)
Allo-SCT for MDS and Blasts %

Sierra, Blood 2002
(sibling)
What kind of cytoreduction is to be used prior to Allo-SCT in MDS patients?

• Intensive chemotherapy?

• Azacytidine?

• Other....?
Hypomethylating agents (Azacitidine/Decitabine) prior to allo-SCT: rationale

- Demethylating agents inhibit DNA methyltransferase and are active in MDS
- Upregulate HLA – molecules and tumor specific antigens, such as cancer testis antigens which could selectively enhance a GVL effect
- Induction of KIR-receptor on NK-cells
- Increased expression of known Minor antigens
- Increased FoxP3 expression and Treg generation
Some results of hypomethylating agents prior to allo-SCT for MDS


- McCarthy JM, et al: 5 Azacytidine prior to allogeneic transplantation **effectively reduces relapse, TRM and overall mortality** in high-risk myelodysplastic and secondary AML. Bone Marrow Transplant; 41:S212-S213. #P746 [abstr.], 2008


Impact of Azacitidine Before Allogeneic Stem-Cell Transplantation for Myelodysplastic Syndromes: A Study by the Société Française de Greffe de Moelle et de Thérapie-Cellulaire and the Groupe-Francophone des Myélodysplasies


http://jco.ascopubs.org/cgi/doi/10.1200/JCO.2012.44.3499
Published Ahead of Print on October 29, 2012 as 10.1200/JCO.2012.44.3499
# OUTCOME

<table>
<thead>
<tr>
<th></th>
<th>Total (163)</th>
<th>5-Aza (n= 48)</th>
<th>Induction CT (n= 98)</th>
<th>5-Aza + Induction (n= 17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-year OS</td>
<td>48%</td>
<td>55%</td>
<td>48%</td>
<td>32%</td>
</tr>
<tr>
<td>3-year EFS</td>
<td>42%</td>
<td>42%</td>
<td>44%</td>
<td>29%</td>
</tr>
<tr>
<td>3-year Relapse</td>
<td>37%</td>
<td>40%</td>
<td>37%</td>
<td>35%</td>
</tr>
<tr>
<td>3-year NRM</td>
<td>21%</td>
<td>19%</td>
<td>20%</td>
<td>35%</td>
</tr>
</tbody>
</table>
OUTCOME
With the goal of down-staging underlying disease and bridging time to transplantation:

- A hypomethylating agent alone appears to be a valid therapeutic approach in MDS patients prior to allo-SCT
How can we capitalize on the long term benefits of allo-SCT?

Can we deliver post-remission therapy in this setting?

1 - Pharmacologic maintenance post allo-SCT

2- Immunotherapy

3- Combinations of both
Azacitidine after allo-SCT: the good without the bad?

Mohamad Mohty and Patrice Chevallier  CHU DE NANTES
5-Azacitidine +/- DLI post transplant
Azacitidine salvage therapy after allo-SCT in AML

CD8+ T cell responses were detected to the majority of tumor antigen peptides

Frequency of tumor-specific CD8+ T cells in paired blood and BM samples from 4 patients during the course of AZA administration

Goodyear et al., Blood 2012
Recommendations of the ELN

Intermediate-2 or High IPSS risk

- >65-70 yrs or poor performance status
  - Supportive care
  - Azacitidine

- <65-70 yrs Good performance status
  - No suitable stem cell donor
    - Poor risk cytogenetics
      - Azacitidine
    - >10% BM blasts, no poor risk cytogenetics
      - AML-like CT OR azacitidine
      - within clinical trial or prospective registry
      - AML-like CT OR azacitidine
    - <10% BM blasts
      - Allo-SCT
    - >10% BM blasts
      - Allo-SCT
"ALLOGENEIC STEM CELL TRANSPLANTATION FOR ACUTE LYMPHOBLASTIC LEUKEMIA"
## Contemporary Treatment of ALL

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Median Age, Year (Range)</th>
<th>Ph+, %</th>
<th>T Cell, %</th>
<th>CR, %</th>
<th>DFS %</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRC/ECOG E2993</td>
<td>1826</td>
<td>31 (15-65)</td>
<td>19</td>
<td>20</td>
<td>91</td>
<td>38 at ≥3 y.</td>
</tr>
<tr>
<td>CALGB 19802</td>
<td>163</td>
<td>41 (16-82)</td>
<td>18</td>
<td>–</td>
<td>78</td>
<td>35 at 3 y.</td>
</tr>
<tr>
<td>GIMEMA ALL 0288</td>
<td>778</td>
<td>27.5 (12.0-60.0)</td>
<td>22</td>
<td>22</td>
<td>82</td>
<td>29 at 9 y.</td>
</tr>
<tr>
<td>GMALL 05/93</td>
<td>1163</td>
<td>35 (15-65)</td>
<td>24</td>
<td>24</td>
<td>83</td>
<td>35-40 at 5 y.</td>
</tr>
<tr>
<td>GOELAMS 02</td>
<td>198</td>
<td>33 (15-59)</td>
<td>22</td>
<td>21</td>
<td>86</td>
<td>41 at 6 y.</td>
</tr>
<tr>
<td>Hyper-CVAD</td>
<td>288</td>
<td>40 (15-92)</td>
<td>17</td>
<td>13</td>
<td>92</td>
<td>38 at 5 y.</td>
</tr>
<tr>
<td>JALSG-ALL93</td>
<td>263</td>
<td>31 (15-59)</td>
<td>22</td>
<td>21</td>
<td>78</td>
<td>30 at 6 y.</td>
</tr>
<tr>
<td>LALA-94</td>
<td>922</td>
<td>33 (15-55)</td>
<td>23</td>
<td>26</td>
<td>84</td>
<td>36 at 5 y.</td>
</tr>
</tbody>
</table>

Prognostic factors in adult ALL

- Age
- Immunophenotype
- White blood cell count at diagnosis
- Cytogenetic markers
- Molecular markers
- Time to complete remission (CR)
Allogeneic Stem Cell Transplantation for Adult ALL
Is there a GvL effect in ALL? **YES** - First clinical description of GvL in humans was in ALL!  

Weiden PL et al. 1979
Yes - potent GvL in ALL in CR1

**Ph\textsuperscript{neg} high risk**

- No donor: 63%
- Donor: 37%
- n=261
- n=204
- p = <.00005

**Ph\textsuperscript{neg} standard risk**

- No donor: 49%
- Donor: 24%
- n=323
- n=239
- p = <.00005

Goldstone et al 2008
## “Donor” vs. “No donor” comparisons

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>No. of Patients</th>
<th>CR Rate</th>
<th>Allogeneic HSCT Strategy*</th>
<th>DFS</th>
<th>HSCT Realization†</th>
<th>HSCT Outcome (by intention)‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>CALGB 9111⁴</td>
<td>1998</td>
<td>198</td>
<td>167</td>
<td>85</td>
<td>46%, 3 years</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>SWOG 8417/8419⁵</td>
<td>2001</td>
<td>353</td>
<td>218</td>
<td>62</td>
<td>25%-32%, 5 years</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>NILG 08/96⁷</td>
<td>2001</td>
<td>121</td>
<td>102</td>
<td>84</td>
<td>48%, 3 years</td>
<td>Allogeneic 21 (29%), autologous 28 (39%)</td>
<td>DFS donor 38% v no donor 43% (P = NS)</td>
</tr>
<tr>
<td>JALSG 93⁷</td>
<td>2002</td>
<td>263</td>
<td>205</td>
<td>78</td>
<td>30%, 6 years</td>
<td>Allogeneic 51 (25%)</td>
<td>—</td>
</tr>
<tr>
<td>Sweden³⁸</td>
<td>2002</td>
<td>153</td>
<td>131</td>
<td>86</td>
<td>30%, 5 years</td>
<td>Allogeneic 26 (20%), autologous 10 (8%)</td>
<td>—</td>
</tr>
<tr>
<td>GIMEMA 02/88⁸</td>
<td>2002</td>
<td>767</td>
<td>627</td>
<td>82</td>
<td>33%, 9 years</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>MDACC¹¹</td>
<td>2004</td>
<td>288</td>
<td>269</td>
<td>92</td>
<td>38%, 5 years</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>EORTC ALL³⁹</td>
<td>2004</td>
<td>340</td>
<td>253</td>
<td>74</td>
<td>36%, 6 years</td>
<td>Allogeneic 49 (19%)</td>
<td>DFS donor 38% v no donor 37% (P = NS)</td>
</tr>
<tr>
<td>LALA 94¹²</td>
<td>2004</td>
<td>922</td>
<td>771</td>
<td>84</td>
<td>30%, 5 years</td>
<td>Allogeneic 145 (36%), autologous 159 (41%)</td>
<td>Ph+: DFS donor 45% v no donor 18% (P = .007)</td>
</tr>
<tr>
<td>GOELAL 02⁸</td>
<td>2004</td>
<td>198</td>
<td>170</td>
<td>86</td>
<td>NR</td>
<td>Allogeneic 41 (24%), autologous 91 (53%)</td>
<td>OS allogeneic SCT 75% v autologous SCT 43% (P = .002)</td>
</tr>
<tr>
<td>PETHEMA ALL-93⁹</td>
<td>2005</td>
<td>222</td>
<td>183</td>
<td>82</td>
<td>35%, 5 years</td>
<td>Allogeneic 57 (31%), autologous 31 (17%)</td>
<td>DFS donor 33% v no donor 39% (P = NS)</td>
</tr>
<tr>
<td>GMALL 07¹⁵</td>
<td>2007</td>
<td>713</td>
<td>635</td>
<td>89</td>
<td>NR</td>
<td>SCT feasibility 70% (allogeneic + autologous)</td>
<td>—</td>
</tr>
<tr>
<td>MRC-ECOG¹⁰</td>
<td>2008</td>
<td>1,646 (Ph+), 484</td>
<td>90</td>
<td>All patients with donor and age &lt; 55; others CHT v autologous SCT</td>
<td>NR</td>
<td>Allogeneic 320 (21%), autologous 162 (11%);</td>
<td>OS donor 53% v no donor 45% (P = .01)</td>
</tr>
<tr>
<td>HOVON¹⁴</td>
<td>2009</td>
<td>433</td>
<td>288</td>
<td>All patients with donor and age &lt; 55; others to autologous SCT</td>
<td>NR</td>
<td>Allogeneic 122 (42%), autologous 126 (44%)</td>
<td>DFS donor 60% v no donor 42% (P = .01)</td>
</tr>
</tbody>
</table>
Allogeneic transplantation for ALL in CR1

HOVON Study

Event-free Survival %

All patients

Donor n = 105
54%

No donor n = 189
37%

p=0.004

Cornelissen JJ, Blood, 2009
Allogeneic transplantation for ALL in CR1

HOVON Study

Standard-risk

Donor  n = 69  60%

No donor  n = 101  41%

Event-free survival %

P=0.02

Years

Cornelissen JJ, Blood, 2009
Effect of donor versus no donor on time to relapse in each trial

<table>
<thead>
<tr>
<th>Trial</th>
<th>Relapses/Patients</th>
<th>Statistics (O-E)</th>
<th>O.R. &amp; 99% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Donor</td>
<td>No donor</td>
<td>Var.</td>
</tr>
<tr>
<td>MRC ALL XA</td>
<td>23/47</td>
<td>62/87</td>
<td>-8.7</td>
</tr>
<tr>
<td>PMH 92</td>
<td>15/34</td>
<td>19/36</td>
<td>-0.5</td>
</tr>
<tr>
<td>JALSG-ALL93</td>
<td>17/32</td>
<td>49/97</td>
<td>1.9</td>
</tr>
<tr>
<td>GRAALL 2003</td>
<td>11/44</td>
<td>35/88</td>
<td>-5.0</td>
</tr>
<tr>
<td><strong>Subtotal:</strong></td>
<td><strong>66/157</strong></td>
<td><strong>165/308</strong></td>
<td><strong>-12.4</strong></td>
</tr>
<tr>
<td></td>
<td>(42.0%)</td>
<td>(53.6%)</td>
<td></td>
</tr>
<tr>
<td>Test for heterogeneity between trials:</td>
<td>$\chi^2 = 3.5$;</td>
<td>$P = 0.3$</td>
<td></td>
</tr>
</tbody>
</table>

| 01b: Donor v no-donor (auto):         |                   |                  |               |                   | |
| HOVON 18 ALL                           | 9/38              | 33/58            | -9.3          | 10.2              | 0.40 (0.18, 0.90) |
| GOELAL02                               | 1/33              | 47/95            | -14.3         | 10.0              | 0.24 (0.11, 0.54) |
| NILG ALL08/96                          | 8/18              | 13/27            | -0.1          | 5.0               | 0.98 (0.31, 3.11) |
| HOVON 37 ALL                           | 13/54             | 58/106           | -12.4         | 16.2              | 0.46 (0.24, 0.88) |
| **Subtotal:**                          | **31/141**        | **151/286**      | **-36.1**     | **41.4**          | **0.42 (0.31, 0.57)** |
|                                         | (22.0%)           | (52.8%)          |               |                   | 2P < 0.00001 |
| Test for heterogeneity between trials: | $\chi^2 = 6.8$;  | $P = 0.08$       |               |                   | |

| 01c: Donor v no-donor (chemo/auto):   |                   |                  |               |                   | |
| EORTC 06861                            | 26/67             | 84/153           | -9.2          | 23.9              | 0.68 (0.40, 1.15) |
| UKALLXII/E2993                         | 110/453           | 375/740          | -78.6         | 115.0             | 0.50 (0.40, 0.64) |
| PETHEMA ALL93                          | 37/70             | 33/84            | 5.0           | 17.3              | 1.33 (0.72, 2.48) |
| LALA-94                                | 40/116            | 111/174          | -25.8         | 36.9              | 0.50 (0.33, 0.78) |
| EORTC ALL-4/06951                      | 35/93             | 70/120           | -11.4         | 25.9              | 0.64 (0.39, 1.07) |
| **Subtotal:**                          | **248/799**       | **673/1271**     | **-120.0**    | **219.0**         | **0.58 (0.51, 0.66)** |
|                                         | (31.0%)           | (53.0%)          |               |                   | 2P < 0.00001 |
| Test for heterogeneity between trials: | $\chi^2 = 16.0$; | $P = 0.003$      |               |                   | |
| **Total:**                              | **345/1097**      | **989/1865**     | **-168.5**    | **310.5**         | **0.58 (0.52, 0.65)** |
|                                         | (31.4%)           | (53.0%)          |               |                   | 2P < 0.00001 |

* 99% or 95% limits

Test for heterogeneity (13 trials): $\chi^2_{12} = 35.2$; $P = 0.0004$
Test for heterogeneity between subtotals: $\chi^2 = 8.9$; $P = 0.01$
Effect of donor versus no donor on TRM in each trial.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Deaths/Patients</th>
<th>Statistics</th>
<th>O.R. &amp; 99% CI</th>
<th>Test for heterogeneity between trials: $\chi^2 = $</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Donor</td>
<td>No donor</td>
<td>O-E</td>
<td>Var.</td>
</tr>
<tr>
<td>01a: donor v no-donor (chemo):</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MRC ALL XA</td>
<td>11/47</td>
<td>7/87</td>
<td>4.0</td>
<td>4.2</td>
</tr>
<tr>
<td>PMH 92</td>
<td>7/34</td>
<td>0/36</td>
<td>3.8</td>
<td>1.7</td>
</tr>
<tr>
<td>JALS-G—ALL93</td>
<td>7/32</td>
<td>9/97</td>
<td>3.4</td>
<td>2.8</td>
</tr>
<tr>
<td>GRAALL 2003</td>
<td>5/44</td>
<td>8/88</td>
<td>0.6</td>
<td>2.9</td>
</tr>
<tr>
<td></td>
<td><strong>Subtotal:</strong></td>
<td></td>
<td>11.8</td>
<td>11.7</td>
</tr>
<tr>
<td>01b: donor v no-donor (auto):</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HOVON 18 ALL</td>
<td>7/36</td>
<td>5/58</td>
<td>1.5</td>
<td>2.9</td>
</tr>
<tr>
<td>GOELAL02</td>
<td>4/33</td>
<td>9/95</td>
<td>-0.2</td>
<td>2.8</td>
</tr>
<tr>
<td>NILG ALL08/96</td>
<td>3/18</td>
<td>2/27</td>
<td>1.1</td>
<td>1.2</td>
</tr>
<tr>
<td>HOVON 37 ALL</td>
<td>9/54</td>
<td>4/106</td>
<td>4.3</td>
<td>2.9</td>
</tr>
<tr>
<td></td>
<td><strong>Subtotal:</strong></td>
<td></td>
<td>6.7</td>
<td>9.8</td>
</tr>
<tr>
<td>01c: donor v no-donor (chemo/auto):</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EORTC 06861</td>
<td>17/67</td>
<td>15/153</td>
<td>6.6</td>
<td>7.0</td>
</tr>
<tr>
<td>UKALLXII/E2993</td>
<td>130/453</td>
<td>79/740</td>
<td>49.1</td>
<td>49.5</td>
</tr>
<tr>
<td>PETHEMA ALL93</td>
<td>6/70</td>
<td>11/84</td>
<td>-1.9</td>
<td>4.2</td>
</tr>
<tr>
<td>LALA-94</td>
<td>26/116</td>
<td>24/174</td>
<td>3.4</td>
<td>12.1</td>
</tr>
<tr>
<td>EORTC ALL—4/06951</td>
<td>24/93</td>
<td>5/120</td>
<td>11.0</td>
<td>7.2</td>
</tr>
<tr>
<td></td>
<td><strong>Subtotal:</strong></td>
<td></td>
<td>68.3</td>
<td>79.9</td>
</tr>
<tr>
<td>Test for heterogeneity between trials: $\chi^2 = 15.4; P = 0.004$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total:</td>
<td>256/1097</td>
<td>178/1865</td>
<td>86.9</td>
<td>101.4</td>
</tr>
</tbody>
</table>

* 99% or 95% limits

Test for heterogeneity (13 trials): $\chi^2_{12} = 23.9; P = 0.02$

Test for heterogeneity between subtotals: $\chi^2 = 0.6; P = 0.8$

Descriptive curve of overall survival by donor versus no donor

Annual event rates:

<table>
<thead>
<tr>
<th>Donor</th>
<th>years 1–5 (%)</th>
<th>years 6+ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No donor</td>
<td>82.5%</td>
<td>78.7%</td>
</tr>
<tr>
<td>Donor</td>
<td>15.3%</td>
<td>1.8%</td>
</tr>
</tbody>
</table>

- allocated Donor (% ± s.d.)
- allocated No donor (% ± s.d.)

Estimated percentage still not suffering Death

Death/person-years:
- Treatment:
  - Donor: 230/1008, 174/737, 66/614, 31/339, 16/442, 35/1081
  - No donor: 342/1738, 468/1267, 162/982, 85/867, 29/544, 50/2445

How to define the Risk?

→ Can be defined **BEFORE** treatment

→ and/or redefined **DURING** treatment:

  - MRD, which can possibly better define transplant candidates

  - Steroid pre treatment
Allo-SCT for adult ALL: Issues to consider in 2014

- Use of RIC transplants and alternative donors
- Transplant after relapse
- Use of MRD analysis
LFS according to the status at transplant after RIC for ALL

Follow-up, median (range): 2.8 y (0.4-6.3)

Mohty et al., Haematologica 2008
RIC allo-SCT with cord blood: Transplantation outcomes

Transplant for Ph pos patients
The Pre-Imatinib Era: JALSG Study

Ph+ ALL Treatment Evolution

- Ph+ ALL historically the most uncontested indication for sibling allogeneic BMT
  - Classic indication for MUD transplantation
  - Cure rate: 25% to 50%

- Advent of imatinib modified the standard of care in ALL
  - ↑ CR rate → more eligible for BMT
  - ↑ number of survivors without BMT
Allo-SCT for adult ALL: Issues to consider in 2014

- Use of RIC transplants
- Transplant after relapse
- Use of MRD analysis
OS of 609 patients who relapsed after MRC/ECOG protocol

Percent surviving

Years

Fielding et al 2007
Outcome after relapse: influence of therapy received after relapse

- Sib Allograft
- MUD Allograft
- Autograft
- Chemotherapy

% surviving

Years

p < 0.00001

Fielding et al 2007
Allo-SCT for adult ALL: Issues to consider in 2014

- Use of RIC transplants
- Transplant after relapse
- Use of MRD analysis and molecular markers
# Cytogenetic, Molecular and Immunologic Markers of Prognostic Significance in Adult ALL

<table>
<thead>
<tr>
<th>Cytogenetics</th>
<th>Molecular Markers</th>
<th>Immunologic Surface Markers</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>t(9;22) (q24; q11.2)</strong></td>
<td>BCR-ABL fusion</td>
<td>CD20</td>
<td>Poor prognosis</td>
</tr>
<tr>
<td><strong>t(4;11) (q21;q23)</strong></td>
<td>MLL-AF4 fusion</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>t(8;14) (q24.1; q32)</strong></td>
<td>BAALC gene</td>
<td>Immature T-cell</td>
<td></td>
</tr>
<tr>
<td>Low hypodiploidy/near triploidy</td>
<td>IKAROS gene</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complex karyotype</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>t(1;19) (q21;p13.3)</strong></td>
<td>NOTCH1</td>
<td></td>
<td>Conflicting data</td>
</tr>
<tr>
<td></td>
<td>FBXW7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High hyperdiploidy Del (9q)</td>
<td></td>
<td></td>
<td>Better prognosis</td>
</tr>
</tbody>
</table>
Can MRD studies indicate which patients should have a transplant and which not?

- Vast majority of patients with adult ALL can have molecular targets identified
- MRD can be identified at different times in the disease and potentially identify different risk groups
- MRD relevance at any time point is dependent on specific prior therapy and possibly cannot be extrapolated from one protocol to another
The Future

- Will novel monoclonal antibodies and immunotherapeutic tools change treatment algorithm for ALL?
Monoclonal Antibody-Based “bridging” Therapies in the Treatment of ALL prior to allo-SCT

<table>
<thead>
<tr>
<th>Antibody Construct</th>
<th>Clinical Trial</th>
<th>Patient Population</th>
<th>Response Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituximab</td>
<td>MDACC(^5)</td>
<td>Newly diagnosed</td>
<td>OS 75% (3 yr)</td>
</tr>
<tr>
<td></td>
<td>GMALL(^6)</td>
<td>Newly diagnosed</td>
<td>OS 71% (5 yr)</td>
</tr>
<tr>
<td>Epratuzumab</td>
<td>COG(^9)</td>
<td>REL/REF</td>
<td>CR 75%</td>
</tr>
<tr>
<td></td>
<td>SWOG(^11)</td>
<td>REL/REF</td>
<td>CR 50%</td>
</tr>
<tr>
<td>Inotuzumab ozogamicin</td>
<td>MDACC(^16)</td>
<td>REL/REF</td>
<td>OR 55%</td>
</tr>
<tr>
<td>Blinatumomab</td>
<td>GMALL(^19)</td>
<td>MRD positive</td>
<td>MRD negative 80%</td>
</tr>
<tr>
<td></td>
<td>GMALL(^20)</td>
<td>REL/REF</td>
<td>CR/CRh 72%</td>
</tr>
<tr>
<td>Moxetumomab</td>
<td>NCI(^23)</td>
<td>REL/REF</td>
<td>OR 29%</td>
</tr>
<tr>
<td>Combotox</td>
<td>Pediatric(^24)</td>
<td>REL/REF</td>
<td>CR 17%</td>
</tr>
</tbody>
</table>
Blinatumomab For Resistant ALL

Disease Free Survival (%)

Time (days)

n = 20

Topp MS, JCO, 2011
Long-term follow-up of hematologic relapse-free survival in a phase 2 study of blinatumomab in patients with MRD in B-lineage ALL

Hematologic RFS. (A) For all 20 evaluable patients, median follow-up was 32.9 months and the lower limit of the 95% confidence interval for median follow-up was 19.1 months. (B) For the 9 HSCT patients, the median follow-up was 32.9 months and the lower limit of the 95% confidence interval for median follow-up was 31.1 months. (C) For the 11 patients not receiving HSCT, the median follow-up was 30.8 months and the lower limit of the 95% confidence interval for median follow-up was 5.1 months.
Conclusions and Perspectives

- Will all high risk old ALL patients in 1st CR benefit from RIC?

- Issues yet to be investigated:
  - the optimal chemotherapy to be applied prior to RIC
  - the type of RIC regimen
  - quality of life

- The role of alternative donors is yet to be established

- Will adolescents and young adults revert to chemotherapy rather than transplant?

- Designing maintenance strategies after RIC allo-SCT, may further improve the outcome of adult ALL.

- Will MRD analysis and molecular markers reduce the use of allograft in this disease?

- New MoAb and immunotherapy tools are changing the landscape of ALL therapy
THANK YOU