ALLOGENEIC STEM CELL TRANSPLANTATION FOR ACUTE MYELOBLASTIC LEUKEMIAS

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CIC de Biotherapie de Marseille
Université de la Méditerranée
Marseille, France
<table>
<thead>
<tr>
<th>Disease</th>
<th>Disease status</th>
<th>Sibling donor</th>
<th>well-matched unrelated</th>
<th>mm unrelated &gt;1 ag</th>
<th>mm related</th>
</tr>
</thead>
<tbody>
<tr>
<td>AML</td>
<td>CR1 (low risk*)</td>
<td>CO/II</td>
<td>D/II</td>
<td>GNR/II</td>
<td>CO/I</td>
</tr>
<tr>
<td></td>
<td>CR1 (intermediate*)</td>
<td>S/II</td>
<td>CO/II</td>
<td>D/II</td>
<td>S/I</td>
</tr>
<tr>
<td></td>
<td>CR1 (high risk*)</td>
<td>S/II</td>
<td>S/II</td>
<td>CO/II</td>
<td>CO/I</td>
</tr>
<tr>
<td></td>
<td>CR2</td>
<td>S/II</td>
<td>S/II</td>
<td>CO/II</td>
<td>CO/II</td>
</tr>
<tr>
<td></td>
<td>CR3, incipient relapse</td>
<td>S/III</td>
<td>CO/III</td>
<td>D/III</td>
<td>GNR/III</td>
</tr>
<tr>
<td></td>
<td>M3 Molecular persistence</td>
<td>S /II</td>
<td>CO /II</td>
<td>GNR/III</td>
<td>GNR/III</td>
</tr>
<tr>
<td></td>
<td>M3 Molecular CR2</td>
<td>S/II</td>
<td>CO/II</td>
<td>GNR/III</td>
<td>S/II?</td>
</tr>
<tr>
<td></td>
<td>Relapse or refractory</td>
<td>CO/II</td>
<td>D/II</td>
<td>D/II</td>
<td>GNR</td>
</tr>
</tbody>
</table>

Table 2: Proposed classification of transplant procedures for adults – 2009: leukaemia
Early Allogeneic Stem-Cell Transplantation for Young Adults With Acute Myeloblastic Leukemia in First Complete Remission: An Intent-to-Treat Long-Term Analysis of the BGMT Experience


J Clin Oncol 23:7676-7684. © 2005
# Allo SCT for CR1 AML

## Deaths

<table>
<thead>
<tr>
<th>Group</th>
<th>Donor/Patients</th>
<th>No donor/Patients</th>
<th>Statistics</th>
<th>HR &amp; 95% CI</th>
<th>Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Donor</td>
<td>No donor</td>
<td>O-E Var</td>
<td>(Donor : No donor)</td>
<td>(SD)</td>
</tr>
<tr>
<td>MRC</td>
<td>158/333</td>
<td>348/639</td>
<td>-11.5 110.0</td>
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<td></td>
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<tr>
<td>EORTC</td>
<td>106/293</td>
<td>187/441</td>
<td>-10.6 66.9</td>
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<td></td>
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<tr>
<td>BGMT</td>
<td>85/182</td>
<td>160/290</td>
<td>-12.2 58.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HOVON</td>
<td>157/326</td>
<td>326/599</td>
<td>-12.2 108.0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

## Cytogenetic risk

<table>
<thead>
<tr>
<th>Class</th>
<th>Donor/Patients</th>
<th>No donor/ Patients</th>
<th>Statistics</th>
<th>HR &amp; 95% CI</th>
<th>Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favorable</td>
<td>57/169</td>
<td>74/311</td>
<td>9.8 30.9</td>
<td>310.7</td>
<td></td>
</tr>
<tr>
<td>Not favorable</td>
<td>360/748</td>
<td>789/1372</td>
<td>-44.2 255.7</td>
<td>235.7</td>
<td></td>
</tr>
<tr>
<td>Intermediate</td>
<td>269/603</td>
<td>601/1106</td>
<td>-36.8 197.1</td>
<td>160.7</td>
<td></td>
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<tr>
<td>Normal,-Y</td>
<td>116/279</td>
<td>227/458</td>
<td>-12.5 80.5</td>
<td>160.7</td>
<td></td>
</tr>
<tr>
<td>Unfavorable</td>
<td>91/145</td>
<td>188/266</td>
<td>-7.4 58.6</td>
<td>160.7</td>
<td></td>
</tr>
</tbody>
</table>

## Age

<table>
<thead>
<tr>
<th>Age</th>
<th>Donor/Patients</th>
<th>No donor/ Patients</th>
<th>Statistics</th>
<th>HR &amp; 95% CI</th>
<th>Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Donor</td>
<td>No donor</td>
<td>O-E Var</td>
<td>(Donor : No donor)</td>
<td>(SD)</td>
</tr>
<tr>
<td>15-35</td>
<td>204/539</td>
<td>473/951</td>
<td>-48.8 152.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>35+</td>
<td>302/595</td>
<td>548/1018</td>
<td>2.3 190.6</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total: 506/1134 (45%) 1021/1969 (52%)
Allo SCT

**Donor**
- Match sibling

**Stem Cell Source**
- Bone Marrow

**Dis. Status**
- CR1
- CRn
- advanced

**Conditioning**
- Standard Myeloablative
  - TBI
  - No TBI

**Patient**

**GVHD prophylaxis**
- CSA
- CSA + MTX

**Disease**
- Cytology
Allo SCT

**Donor**
- Match sibling
- Match unrelated / MM unrelated
  - Typing resolution
    - 6/6 vs 10/10
- MM Sibling

**Stem Cell Source**
- Bone Marrow
- PBSC
- Cord Blood

**Dis. Status**
- CR1
- CRn
- advanced

**Patient**
- Age
- Comorbidities

**Conditioning**
- Standard Myeloablative
  - TBI
  - No TBI
- Reinforced Myeloablative
- Reduced intensity
- Non Myeloablative

**Disease**
- Cytology
- Gen Abnormality
- Response to Trt

**GVHD prophylaxis**
- CSA
- CSA + MTX
- others
- Ex vivo T Cell depletion
- ATG
### Allo SCT

#### Donor
- **Match sibling**
- **Match unrelated / MM unrelated**
  - Typing resolution
  - 6/6 vs 10/10
- **MM Sibling**

#### Stem Cell Source
- **Bone Marrow**
- **PBSC**
- **Cord Blood**

#### Patient
- **Age**
- **Comorbidities**

#### Conditioning
- **Standard Myeloablative**
  - TBI
  - No TBI
- **Reinforced Myeloablative**
- **Reduced intensity**
- **Non Myeloablative**

#### Dis. Status
- **CR1**
- **CRn**
- **advanced**

#### Disease
- **Cytology**
- **Gen Abnormality**
- **Response to Trt**

#### GVHD prophylaxis
- **CSA**
- **CSA + MTX**
- **others**
- **Ex vivo T Cell depletion**
- **ATG**
Historical markers in the development of allogeneic hematopoietic cell transplantation

E. Demetra Thomas,¹ Karl G. Blume²

1949–1951: THE HUMORAL HYPOTHESIS

1954–1956: THE CELLULAR HYPOTHESIS

1956–1959: ADVANCES IN MARROW GRAFTING TECHNOLOGY THROUGH ANIMAL STUDIES


1960–1967: PESSIMISM ABOUT ALLOGENEIC MARROW GRAFTING IN HUMAN PATIENTS BUT PROGRESS IN ANIMAL MODELS OF ALLOGENEIC MARROW GRAFTING


1976–1986: WIDENING APPLICATION OF ALLOGENEIC MARROW GRAFTING FOR HUMAN PATIENTS

1986–PRESENT: HEMATOPOIETIC CELL TRANSPLANTATION AS STANDARD THERAPY

1999–? ?

TBI

No TBI?
The ideal preparative regimen for marrow transplantation of patients with malignant diseases should:

- Be capable of eradicating malignancy
- Have tolerable morbidity without mortality
- Have sufficient immunosuppressive effect ... to avoid graft rejection

The search for an ideal preparative regimen serving all these purposes have been a major focus ... over the past 20 years

No ideal preparative regimen currently exists

Finn B. Petersen and Scott I. Bearman
Preparative regimens and their toxicity
In Bone Marrow transplantation
by SJ Forman, KG Blume and E Donnall Thomas, 1994
Which myeloablative conditioning regimen: TBI or Busulfan based regimen?

- Main concern of early days = engraftment.

- **Total Body Irradiation:**
  - Highly myelo-ablative
  - Highly immunosuppressive
  - Few chemical drugs

- **Total Body Irradiation fulfilled expectations:**
  - Animal models
  - Clinical situation
Busulfan plus cyclophosphamide compared with total-body irradiation plus cyclophosphamide before marrow transplantation for myeloid leukemia: long-term follow-up of 4 randomized studies

Gérard Socié, Reginald A. Clift, Didier Blaise, Agnès Devergie, Olle Ringden, Paul J. Martin, Mats Rembrøger, H. Joachim Deeg, Tapani Ruutu, Mauricette Michallet, Keith M. Sullivan, and Sylvie Chevret

Figure 1. Survival and DFS of patients with CML receiving either Bu or TBI associated with CY as conditioning regimen before transplantation.

Figure 2. Survival and DFS of patients with AML receiving either Bu or TBI associated with CY as conditioning regimen before transplantation.
Myeloablative Allogeneic stem cell cell transplantation

- High Leukemia control
- Long term disease control
- Usually high LFS
- Higher survival in selected population

How to achieve better results?
- Higher disease eradication
  - higher TRM
- Attempt to decrease GVHD
  - higher relapse
To decrease TRM by optimizing Conditioning intensity?

Conditioning regimen
- Disease
- Endotoxin

Donor T Cell

Host cells

Donor mononuclear cell

- IL1
- TNF@
- IL2
- IFN-G
Increased Serum Levels of Tumor Necrosis Factor α Precede Major Complications of Bone Marrow Transplantation


*Blood, Vol 75, No 4 (February 15), 1990; pp 1011–1016*
To decrease TRM by optimizing Conditioning intensity?

- Minimal Conditioning?
- Intermediate Myeloablation?
- Reduced toxicity approach?
Achievements after RIC Allo SCT

- N=100
- CR1-2 AL : 100%
- Age: 33 (14-49)
- CDT: MAC = 100%

- N=100
- Age: 50 (18-64)
- CDT: RIC = 100%
- CR1-2 AL+ age < 50: 24%

- 5 year LFS: 53% (42-61)

- 5 year LFS: 60% (48-70)
- 5 year LFS: 69% (48-84)
IS A RIC ALLO-SCT BETTER THAN ANOTHER?
Treatment for Acute Myelogenous Leukemia by Low-dose, Total-body, Irradiation-based conditioning and hematopoietic cell transplantation from related and unrelated donors

- n= 122
- Status: CR 74% (CR1: 42%)
- Donor: MRD: 48%
- Not Eligible for STD ASCT
- AGE: 57 (17-74)
- TBI 2 Gy +/- FLUDA
- CSA + MMF

- NRD: 16% at 2 yrs
- Relapse: 39% at 2 yrs
- OS: 48% at 2 yrs
- LFS: 44% at 2 yrs

U. Hegenbart, R. Storb et al.; JCO, 2006
Nonablative versus reduced-intensity conditioning regimens in the treatment of acute myeloid leukemia and high-risk myelodysplastic syndrome: dose is relevant for long-term disease control after allogeneic hematopoietic stem cell transplantation

Marcos de Lima, Athanasios Anagnostopoulos, Mark Munsell, Munir Shahjahan, Naoto Ueno, Cindy Ippoliti, Borje S. Andersson, James Gajewski, Daniel Couriel, Jorge Cortes, Michele Donato, Joyce Neumann, Richard Champlin, and Sergio Giralt

- **FAI:**
  - FLUDA: 120 mg/m²
  - CYTARABINE: 4 g/m²
  - IDARUBICINE: 36 mg/m²

- **FM**
  - FLUDA: 100-150 mg/m²
  - MELPHALAN: 140 mg/m²

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**Table 5. Estimates of cumulative incidence of mortality at 3 years**

<table>
<thead>
<tr>
<th>Outcome and treatment</th>
<th>Cumulative incidence</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Lower bound</td>
</tr>
<tr>
<td>Relapse-related mortality</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FAI</td>
<td>0.534</td>
<td>0.343</td>
</tr>
<tr>
<td>FM</td>
<td>0.260</td>
<td>0.149</td>
</tr>
<tr>
<td>Non-relapse-related mortality</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FAI</td>
<td>0.156</td>
<td>0.028</td>
</tr>
<tr>
<td>FM</td>
<td>0.392</td>
<td>0.267</td>
</tr>
</tbody>
</table>
Is there an alternative to the toxicity-efficacy dilemma for AMLs?

- **Pre AHSCT chemotherapy**
  - **Induction**
  - **Consolidation**
    - **Intensive consolidation***
      - HIDAC Dauno (60 mg/m²) day 1 and 2; ARAC: 3 g/m² x 2/d over 3 H for 4 days
      - or HIDAC + HDM: Melphalan 140 mg/m²

- **Allogeneic transplant**
  - **FBA (High ATG)**
    - Fludarabine 30 mg/m²
      - X X X X X X
    - Busulfan 4 mg/kg
      - X X
    - ATG * 2,5 mg/kg
      - X X X (X)
  - **FBA (Low ATG)**
    - Fludarabine 30 mg/m²
      - X X X X X X
    - Busulfan 4 mg/kg
      - X X
    - ATG * 2,5 mg/kg
      - X

* THYMOGLOBULINE
### RIC AML for patients with CR1 AML

<table>
<thead>
<tr>
<th>Patient Age</th>
<th>52 (26-60)</th>
</tr>
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<tbody>
<tr>
<td>n= 37</td>
<td></td>
</tr>
<tr>
<td>Patient Age</td>
<td></td>
</tr>
<tr>
<td>Pts with poor leukemic risk</td>
<td></td>
</tr>
<tr>
<td>Poor risk cytogen.</td>
<td>13 (35)</td>
</tr>
<tr>
<td>2 induction courses</td>
<td>10 (27)</td>
</tr>
<tr>
<td>WBC ≥ 30 x 10⁹/l</td>
<td>5 (14)</td>
</tr>
<tr>
<td>M0-M6-M7 FAB</td>
<td>4 (11)</td>
</tr>
<tr>
<td>Secondary leukemia</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Pts with high clinical risk</td>
<td>26 (70)</td>
</tr>
<tr>
<td>Age &gt; 50</td>
<td>22 (59)</td>
</tr>
<tr>
<td>Serious comorbidities</td>
<td>10 (30)</td>
</tr>
</tbody>
</table>

| Follow-up: months            | 36 (16-70) |
| Non relapse deaths           |            |
| Days                         | 8% (0-17)  |
| Relapse                      |            |
| Days                         | 22% (9-35) |
| 4Y Overall Survival          |            |
| Non relapse deaths           | 89,176,1067|
| Relapse                      | 143 (71-566)|
| 4Y Overall Survival          | 67% (49-81)|
| 2 Year LFS                   | 68% (50-80)|

*Blaise et al, Cancer 2005, updated*

![Graph showing no cGVHD and cGVHD with P=0.003](image)

No cGVHD

P=0.003

cGVHD
The role of reduced intensity conditioning allogeneic stem cell transplantation in patients with acute myeloid leukemia: a donor vs no donor comparison

M Mohty¹,²,³,⁶, H de Lavallade¹,⁶, P Ladrique⁴, C Faucher¹,², N Vey², D Coso², A-M Stoppa², J-A Gastaut²,⁵ and D Blaise¹,²,³,⁵

Table 1 Patients' characteristics and acute myeloid leukemia features

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No 'donor' group n = 60 (%)</th>
<th>'Donor' group n = 35 (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), median (range)</td>
<td>52 (26-61)</td>
<td>52 (26-65)</td>
<td>NS</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>32 (53)</td>
<td>15 (43)</td>
<td>NS</td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>De novo AML</td>
<td>44 (73)</td>
<td>29 (83)</td>
<td>NS</td>
</tr>
<tr>
<td>Secondary AML</td>
<td>16 (27)</td>
<td>6 (17)</td>
<td>NS</td>
</tr>
<tr>
<td>Cytogenetics risk group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermediate</td>
<td>48 (80)</td>
<td>29 (83)</td>
<td>NS</td>
</tr>
<tr>
<td>Poor</td>
<td>12 (20)</td>
<td>6 (17)</td>
<td>NS</td>
</tr>
<tr>
<td>Number of induction courses to achieve CR³</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>One</td>
<td>50 (83)</td>
<td>25 (71)</td>
<td>NS</td>
</tr>
<tr>
<td>Two or more</td>
<td>10 (17)</td>
<td>10 (29)</td>
<td>NS</td>
</tr>
<tr>
<td>FAB subtype</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M0</td>
<td>2 (3)</td>
<td>1 (3)</td>
<td></td>
</tr>
<tr>
<td>M1-M2</td>
<td>27 (45)</td>
<td>19 (54)</td>
<td>NS</td>
</tr>
<tr>
<td>M4-M5</td>
<td>25 (42)</td>
<td>13 (37)</td>
<td>NS</td>
</tr>
<tr>
<td>M6-M7</td>
<td>6 (10)</td>
<td>2 (6)</td>
<td></td>
</tr>
<tr>
<td>Autologous transplantation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median time (days) between diagnosis and autologous transplantation (range)</td>
<td>37 (62)</td>
<td>18 (49)</td>
<td>NS</td>
</tr>
<tr>
<td>High-dose cytarabine chemotherapy</td>
<td>52 (87)</td>
<td>31 (88)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Leukemia (2005) 19, 916-920
ARE FURTHER PROGRESSES ACHIEVABLES?

REDUCED TOXICITY CONDITIONING?
Which benefits with a Busulfan I.V. form?

- **Disease Progression**
  - Distribution frequency
- **Organ Toxicity**
  - Distribution frequency
- **Myeloablation**
  - Distribution frequency

**Drug exposure to busulfan**

**THERAPEUTIC WINDOW**

Courtesy from C Puozzo
IV Busulfan and Cyclophosphamide (IV BuCy2) for hematologic malignancies prior to Allo HSCT: a phase II study

- 61 patients
- Conditioning:
  - IV BU: 0.8 mg/Kg x 16
  - CY: 60 mg/Kg x 2
- Age: 37 (20-63)
- HLA matched-sib
- AML (43%); CML (27%); MDS (15%); NHL/HD (15%)
- Active disease: 75%
- 86% with AUC: 800-1500
- No Graft failure
- T to .5 ANC: 13
- Full D Chimerism: 100%
- 100d TRM: 6/61 (9.8%)
  - Fatal VOD: 2 (1 s\textsuperscript{nd} SCT)
- 2 year OS: 67%
- 2 year DFS: 42%

Andersson et al, BBMT, 8, 145-154, 2002
Targeted BU-CY Program Phase II 3/06

- Patients aged 55-70 years
  - Busulfex: 0.8 mg/kg IV x 16 doses
    → PK on first, 2nd and 13th dose
    → Target an average of 650 ng/ul
  - Cyclophosphamide 60 mg/kg x 2 d
  - HLA-ID or 10/10 matched MUD

- Outcome
  - F/U: 13 (3-28) months
  - TRM:
    → Day 100: 0
    → GVHD related: 1
  - Relapse: 4
  - Alive in CR: 8

- Patient Characteristics
  - 17 enrolled,
  - 13 with Fup > 3 months
    ✓ HLA Ident Sib: 10
    ✓ MUD: 3
  - Age: 59 (55-66)
  - Diagnosis:
    ✓ AML: 9 (CR1: 8/CR2: 1) /MDS: 2/ MM: 2 (after auto)

- Intensive supportive care
  - Palifermin pre- and post prep. regimen
  - Prograf + MMF as GVHD prophylaxis
  - Ursodiol and Enoxeparin for SOS prophylaxis
  - Mould, Candida, gram-neg and CMV ID prophylaxis
  - Higher PRBC Transf. parameters (Hct 28-30%)
  - TPN if needs <50% >3d when indicated
  - PBSC’s used

Salt Lake City Intermountain Blood and Marrow Transplant Program, FB Petersen, MD
Once dialy Intravenous Busulfan and Fludarabine: clinical and pharmacokinetic results of a myeloablative reduced toxicity conditioning regimen for Allo HSCT in AML and MDS

De Lima M. et al., Blood 2004

**Table 1. Patient, disease, and donor characteristics**

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, y (range)</td>
<td>45 (19-66)</td>
</tr>
<tr>
<td>Sex, no. (%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>48 (50)</td>
</tr>
<tr>
<td>Female</td>
<td>48 (50)</td>
</tr>
<tr>
<td>Disease diagnosis, no. (%)</td>
<td></td>
</tr>
<tr>
<td>AML</td>
<td>74 (77)</td>
</tr>
<tr>
<td>MDS</td>
<td>22 (23)</td>
</tr>
<tr>
<td>RA</td>
<td>2</td>
</tr>
<tr>
<td>RAEB</td>
<td>13</td>
</tr>
<tr>
<td>RAEBII</td>
<td>5</td>
</tr>
<tr>
<td>CMMML</td>
<td>2</td>
</tr>
<tr>
<td>Time from diagnosis to transplantation, mo (range)</td>
<td>11.7 (1.9-87.5)</td>
</tr>
<tr>
<td>Disease status at transplantation, no. (%)</td>
<td></td>
</tr>
<tr>
<td>Remission</td>
<td>42 (44)</td>
</tr>
<tr>
<td>Active disease</td>
<td>54 (56)</td>
</tr>
<tr>
<td>First CR</td>
<td>19 (20)</td>
</tr>
<tr>
<td>Second or subsequent CR</td>
<td>23 (24)</td>
</tr>
<tr>
<td>Primary induction failure</td>
<td>20 (21)</td>
</tr>
<tr>
<td>First relapse</td>
<td>21* (22)</td>
</tr>
<tr>
<td>Second or subsequent relapse</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Untreated</td>
<td>10 (10)</td>
</tr>
<tr>
<td>Median duration of first CR, mo (range)</td>
<td>4.5 (0-73.4)</td>
</tr>
<tr>
<td>PB blasts at transplantation, no. (%)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>69 (72)</td>
</tr>
<tr>
<td>Yes</td>
<td>27 (28)</td>
</tr>
<tr>
<td>Cytogenetics, no. (%)</td>
<td></td>
</tr>
<tr>
<td>Good prognosis</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Standard risk</td>
<td>65 (68)</td>
</tr>
<tr>
<td>Poor prognosis</td>
<td>28 (29)</td>
</tr>
<tr>
<td>CMV* recipients, no. (%)</td>
<td>77 (80)</td>
</tr>
<tr>
<td>Donor characteristics, no. (%)</td>
<td></td>
</tr>
<tr>
<td>HLA-identical sibling</td>
<td>56 (55)</td>
</tr>
<tr>
<td>HLA-identical related</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Matched unrelated</td>
<td>36 (38)</td>
</tr>
<tr>
<td>Mismatched related</td>
<td>2 (8)</td>
</tr>
</tbody>
</table>

- **FLUDA**: 40 mg/m²/d x 4
- **BUSILVEX**: 130 mg/m²/d* x 4
- **THYMO**: 0.5, 1, 2 mg/kg D- 3, -2, -1 if MUD

*Busilvex= 3.2 mg/kg/d

**VOD = 0**

**TRM = 1%**
Patients in CR-AML
I.V. BuFlu (FB4) vs. I.V. BuCy2

BuFlu  n= 148 AML (69 CR) and MDS, 53% MRD, 30% bad risk
BuCy2  n= 67 AML (32 CR) and MDS, 79% MRD, 30% bad risk

Significant survival benefit with I.V. BuFlu compared to BuCy2 due to a significant reduction in TRM (7% vs 18%)

de Lima M et al. ASH 2006
Once-Daily Intravenous Busulfan/Fludarabine with Thymoglobulin for Allo SCT from Matched Siblings Using:
A Myeloablative Regimen with Low Nonrelapse Mortality in All But Older Patients with High-Risk Disease

<table>
<thead>
<tr>
<th>Treatment</th>
<th>-6</th>
<th>-5</th>
<th>-4</th>
<th>-3</th>
<th>-2</th>
<th>-1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fludarabine 50 mg/m²</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>IV Busulfan 3.2 mg/kg</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATG 1.5 mg/kg</td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>CSA + MTX (1,3,6,11)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 4. Outcomes at 3 Years by Age and Risk

<table>
<thead>
<tr>
<th></th>
<th>Low-Risk ( \leq 45 \text{ Years} )</th>
<th>Low-Risk ( &gt;45 \text{ Years} )</th>
<th>High-Risk ( \leq 45 \text{ Years} )</th>
<th>High-Risk ( &gt;45 \text{ Years} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>54</td>
<td>31</td>
<td>40</td>
<td>75</td>
</tr>
<tr>
<td>OS</td>
<td>76% ± 6%</td>
<td>83% ± 7%</td>
<td>64% ± 8%</td>
<td>37% ± 7%</td>
</tr>
<tr>
<td>DFS</td>
<td>72% ± 6%</td>
<td>74% ± 8%</td>
<td>43% ± 9%</td>
<td>34% ± 6%</td>
</tr>
<tr>
<td>NRM</td>
<td>4% ± 3%</td>
<td>6% ± 4%</td>
<td>6% ± 4%*</td>
<td>27% ± 7%*</td>
</tr>
<tr>
<td>Relapse</td>
<td>25% ± 6%</td>
<td>21% ± 8%</td>
<td>51% ± 8%</td>
<td>52% ± 6%</td>
</tr>
</tbody>
</table>

*P = .04.
Conclusions

- Allo HSCT remains the standard treatment for intermediate/high risk AML patients.

- How to improve current results: better selection of patients based on:
  - Disease status
  - Cytogenetic risk group
  - Co-morbid conditions
  - Choice of conditioning regimens

- Is there a best conditioning regimen?
  - TBI = Still most commonly used conditioning regimen
  - I.V. Busulfan = an appealing alternative
  - Myeloablative or reduced intensity?
    - Ongoing prospective trials
    - Response might vary: diagnosis, donor
    - IV BU + Flu? “The good from Standard and the good from RIC?”
Allogeneic Marrow Stem-Cell Transplantation From Human Leukocyte Antigen–Identical Siblings Versus Human Leukocyte Antigen–Allelic–Matched Unrelated Donors (10/10) in Patients With Standard-Risk Hematologic Malignancy: A Prospective Study From the French Society of Bone Marrow Transplantation and Cell Therapy

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Patients (N = 236)</th>
<th>Sibling Group (n = 181)</th>
<th>Unrelated Group (n = 55)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recipient age, years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 36.7</td>
<td>118</td>
<td>84</td>
<td>34</td>
<td></td>
</tr>
<tr>
<td>≥ 36.7</td>
<td>118</td>
<td>97</td>
<td>21</td>
<td>.045</td>
</tr>
<tr>
<td>Underlying disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AL</td>
<td>175</td>
<td>141</td>
<td>34</td>
<td>.02</td>
</tr>
<tr>
<td>CML</td>
<td>43</td>
<td>30</td>
<td>13</td>
<td>NS</td>
</tr>
<tr>
<td>MDS</td>
<td>18</td>
<td>10</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Disease status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AL in first complete remission or CML in chronic phase</td>
<td>167</td>
<td>134</td>
<td>33</td>
<td>.045</td>
</tr>
<tr>
<td>Other situations</td>
<td>69</td>
<td>47</td>
<td>22</td>
<td></td>
</tr>
</tbody>
</table>

*Table 1. Main Initial Characteristics of the Patients and Donors (N = 236)*
**Sibling v HLA-Matched Unrelated Allo-SCT**

**A**
- Overall Survival (%)
- Sibling
  - N: 181
  - Deaths: 67
- Unrelated
  - N: 55
  - Deaths: 212
- Cox P = .551

**B**
- Transplantation-Related Mortality (%)
- Sibling
  - N: 181
  - Deaths: 45
- Unrelated
  - N: 55
  - Deaths: 15
- Cox P = .533

**C**
- Event-Free Survival (%)
- Sibling
  - N: 181
  - Deaths: 84
- Unrelated
  - N: 55
  - Deaths: 23
- Cox P = .962

**D**
- Relapse (%)
- Sibling
  - N: 181
  - Deaths: 39
- Unrelated
  - N: 55
  - Deaths: 8
- Cox P = .522
Comparative single-institute analysis of cord blood transplantation from unrelated donors with bone marrow or peripheral blood stem-cell transplants from related donors in adult patients with hematologic malignancies after myeloablative conditioning regimen

Table 1. Characteristics of patients and grafts

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>BMT or PBSCT recipient</th>
<th>CBT recipient</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>40</td>
<td>38</td>
<td>.83</td>
</tr>
<tr>
<td>Range</td>
<td>16-58</td>
<td>16-55</td>
<td></td>
</tr>
</tbody>
</table>

Diagnosis, no. (%)  

<table>
<thead>
<tr>
<th>Diagnosis, no. (%)</th>
<th>BMT or PBSCT recipient</th>
<th>CBT recipient</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>AML</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR1, CR2</td>
<td>8 (11)</td>
<td>26 (26)</td>
<td></td>
</tr>
<tr>
<td>Advanced</td>
<td>23 (32)</td>
<td>31 (31)</td>
<td></td>
</tr>
<tr>
<td>ALL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR1, CR2</td>
<td>7 (10)</td>
<td>9 (9)</td>
<td></td>
</tr>
<tr>
<td>Advanced</td>
<td>10 (14)</td>
<td>11 (11)</td>
<td></td>
</tr>
<tr>
<td>CML</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CP</td>
<td>7 (10)</td>
<td>1 (1)</td>
<td></td>
</tr>
<tr>
<td>Advanced</td>
<td>4 (6)</td>
<td>5 (5)</td>
<td></td>
</tr>
<tr>
<td>MDS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RA</td>
<td>4 (6)</td>
<td>3 (3)</td>
<td></td>
</tr>
<tr>
<td>Advanced</td>
<td>1 (1)</td>
<td>8 (8)</td>
<td></td>
</tr>
<tr>
<td>ML</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR1, CR2</td>
<td>1 (1)</td>
<td>5 (5)</td>
<td></td>
</tr>
<tr>
<td>Advanced</td>
<td>6 (9)</td>
<td>2 (2)</td>
<td></td>
</tr>
</tbody>
</table>
CONCLUSIONS

- Cure is usually offered only once
- Individual prognosis is still to be determined
  - Biomarkers for individual prognosis
- Allo SCT affords long term remission and cure
- Debate remains open
  - Goal of RIC approach: SCT → Immunotherapy
    - Complete chemotherapy approach
    - Search for improvements:
      - Early post Graft Immunomodulation
- 75% patients have no sibling donor
  - RIC and MUD/CB: will NRD be decreased enough?
- The real challenge is the elderly population
SEER Crude Incidence Rates  Leukemia
SEER 13 Registries for 1998-2002
Don’t Forget

- Most of the knowledge we have is based on
  - Patients under 50
  - CR1
  - Myeloablative conditioning
  - Geno identical
  - Bone Marrow

- Do not translate results right away into
  - Elderly patients
  - Advanced Diseases
  - Reduced intensity conditioning
  - Non Geno-identical
  - PBSC and Cord Blood
Science is facts.
Just as houses are made of stones,
so is science made of facts;
but a pile of stones is not a house
and a collection of stones is not
necessarily science.

Henri Poincaré