Thérapeutiques pré-transplantation

Modulation de la dose-intensité / modulation de l’immunossuppression

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Marseille

AIH, Marseille, September, 28th, 2013
**Donor**
- Match sibling or UD
  - 6/6 vs 8/8 vs 10/10
- Mismatched RD or UD

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

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

**Patient**
- Age
- Comorbidities

**Conditioning preparation**
- Standard Myeloablative
  - TBI or No TBI
- Reinforced Myeloablative
- NMAC or RIC or RTC

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

**GVHD prophylaxis**
- CSA / CSA + MTX
- Tacrolimus
- Ex vivo T Cell depletion
- ATG
- HD CY post HSCT

**Allo SCT**
Historical markers in the development of allogeneic hematopoietic cell transplantation

E. Donnall Thomas, Karl G. Blume

1949-1951: The Humoral Hypothesis
1954-1956: The Cellular Hypothesis
1956-1959: Advances in Marrow Grafting Technology through Animal Studies
1956-1959: Recognition of the Potential of Marrow Grafting in the Treatment of Human Disease
1960-1967: Pessimism About Allogeneic Marrow Grafting in Human Patients but Progress in Animal Models of Allogeneic Marrow Grafting
1968-1975: The Beginning of the Modern Era of Human Marrow Transplantation
1976-1986: Widening Application of Allogeneic Marrow Grafting for Human Patients
1986-Present: Hematopoietic Cell Transplantation as Standard Therapy

1999- Now

TBI / BM / Sibling

➢ No TBI
➢ PBSC
➢ UD/CB
➢ RIC
➢ Haplo
Malignancies After Marrow Transplantation for Aplastic Anemia and Fanconi Anemia: A Joint Seattle and Paris Analysis of Results in 700 Patients


Table 4. Predictors of Posttransplant Solid Tumors by Multivariable, Stepwise Proportional Hazards Model

<table>
<thead>
<tr>
<th>Patient Population</th>
<th>Step Entered in Model</th>
<th>Univariable P</th>
<th>Multivariable P</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Azathioprine/chronic</td>
<td>1</td>
<td>.0001</td>
<td>.0005</td>
<td>11.7 (3.9-34.6)</td>
</tr>
<tr>
<td>GHVD*</td>
<td>1</td>
<td>.0001</td>
<td>.0005</td>
<td>11.7 (3.9-34.6)</td>
</tr>
<tr>
<td>Fanconi anemia</td>
<td>2</td>
<td>.0002</td>
<td>.0001</td>
<td>11.2 (3.9-34.6)</td>
</tr>
<tr>
<td>Non-Fanconi patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Azathioprine/chronic</td>
<td>1</td>
<td>.0001</td>
<td>.0043</td>
<td>7.5 (1.8-30.2)</td>
</tr>
<tr>
<td>GVHD*</td>
<td>1</td>
<td>.0001</td>
<td>.0043</td>
<td>7.5 (1.8-30.2)</td>
</tr>
<tr>
<td>Irradiation</td>
<td>2</td>
<td>.0024</td>
<td>.0424</td>
<td>3.9 (1.0-15.0)</td>
</tr>
<tr>
<td>Age</td>
<td>3</td>
<td>.0525</td>
<td>.0252</td>
<td>1.1 (1.0-1.12)</td>
</tr>
</tbody>
</table>

* Azathioprine modeled as a time-dependent variable and assumed to be started at diagnosis of chronic GVHD (see Materials and Methods).
Historical Myeloablative Conditionings
Cytotoxicity and Procedure Toxicity

Holler, E, Blood 1990
Conditioning Regimens History

- Conditioning Regimens History
- Myeloablative RTC
- RIC/NMAC

MAC


- N=1957*
- 1989
- 1986
- 1979

- IV BU/IV Treo
- Purines analogs
- ATG/MMF...

- LD/LBI
Conditioning intensity definition

```
Myeloablative (MA)*
TBI ≥ 5 Gy single dose or ≥ 8 Gy fractionated
Bu > 8 mg/kg orally or intravenous equivalent

Nonmyeloablative (NMA)†
TBI ≤ 2 Gy± purine analog
Flu + Cy ± ATG
Flu + AraC + Ida
Cladribine + AraC
Total Lymphoid Irradiation + ATG
```

- **MA** (Myeloablative): Requires stem cell support, reduces intensity conditioning.
- **RIC** (Reduced intensity conditioning): No stem cell support required.
- **NMA** (Nonmyeloablative): Requires stem cell support, nonablative.

Stem cell support required

Stem cell support required

Non ablative

Non ablative

Minimal

Minimal

Short

Long

Irreversible

Irreversible

Pancytopenia

Pancytopenia
What was/is (were/are) the goal(s)?

- Absence of induced deaths?
  - First step
- Disease control?
  - Of course
- Higher survival and higher cure?
  - Not bad

Survival + Cure + Quality of Survival!
Reduced procedure related toxicity?

Gooley, T, NEJM 2010

Horan, J, J Clin Onco 2011
Reasons for an overall reduced NRM

• Implementation of standard operating procedures
• Improved transplant management
  – Shorter initial neutropenia
  – Effective drug PK
• Improved complication management
  – More effective approaches for GVHD prevention
  – More effective approaches for fungal infections and CMV disease
  – Advances in nephrology, critical care and transfusion medicines
• Better donor selection
  – Improvement in HLA typing and matching
• Better disease monitoring
  – MRD monitoring
• Better patient selection
  – Comorbidities score
• Reduced intensity conditioning?
## Further Reduced NRM after RIC?

<table>
<thead>
<tr>
<th>Study</th>
<th>Dg/ Age</th>
<th>CDT</th>
<th>N</th>
<th>NRM</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Luger, BMT 2011, CIBMTR</strong></td>
<td>AML/MDS 1-82</td>
<td>MAC 37 (1-82)</td>
<td>3731</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>RIC BM 35 (16-69)</td>
<td></td>
<td>273</td>
<td>0.96 (0.77-1.19)</td>
</tr>
<tr>
<td></td>
<td>RIC PBSC 41 (1-78)</td>
<td></td>
<td>768</td>
<td>0.90 (0.77-1.05)</td>
</tr>
<tr>
<td></td>
<td>NMA 41 (19-75)</td>
<td></td>
<td>407</td>
<td>1.05 (0.87-1.28)</td>
</tr>
<tr>
<td><strong>Cornelissen, ASH 2011, Hovon</strong></td>
<td>CR1 AML 45 (40-60)</td>
<td>MAC</td>
<td>237</td>
<td>24% +/- 3</td>
</tr>
<tr>
<td></td>
<td>RIC</td>
<td></td>
<td>144</td>
<td>9% +/- 3</td>
</tr>
<tr>
<td><strong>Lioure, Blood 2012, Goelams</strong></td>
<td>CR1 AML 44 (17-60)</td>
<td>CY-TBI &lt; 50y</td>
<td>117</td>
<td>15.8% (9.8-23)</td>
</tr>
<tr>
<td></td>
<td>F-B-ATG&gt; 50y</td>
<td></td>
<td>47</td>
<td>6.5% (0.2-16)</td>
</tr>
</tbody>
</table>
Reduced early mortality is a mandatory goal
When a patient is gone, he cannot be cured!
RIC allo SCT for patients with AML
Long term results of a “donor” vs. “no donor” comparison

Mohty, M, Leukemia 2009
**RIC vs. Standard CDT before allo HSCT in patients with AML in CR1: a prospective, open-label randomised phase 3 trial**

<table>
<thead>
<tr>
<th></th>
<th>RIC</th>
<th>Standard</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>99</td>
<td>96</td>
<td></td>
</tr>
<tr>
<td>CDT</td>
<td>Flu-TBI (2gy x 4)</td>
<td>Cy-TBI (2gy x 6)</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>45 (18-60)</td>
<td>44 (18-60)</td>
<td></td>
</tr>
<tr>
<td>NRM</td>
<td>13%</td>
<td>18%</td>
<td>0.62 (0.30-1.31)</td>
</tr>
<tr>
<td>Relapse</td>
<td>28%</td>
<td>26%</td>
<td>1.10 (0.63-1.90)</td>
</tr>
<tr>
<td>Survival</td>
<td>61%</td>
<td>58%</td>
<td>0.77 (0.48-1.25)</td>
</tr>
<tr>
<td>DFS</td>
<td>58%</td>
<td>56%</td>
<td>0.85 (0.55-1.32)</td>
</tr>
</tbody>
</table>

Bornhauser, Lancet Oncology, 2012
Randomized trial of MAC regimens
**BUCY vs. BUFLU**

**N**
- BUCY: 64
- BUFLU: 62

**Age**
- BUCY: 41 (17–59)
- BUFLU: 41 (17–59)

**AML/ALL**
- BUCY: 59% / 34%
- BUFLU: 52% / 40%

**CR**
- BUCY: 84%
- BUFLU: 84%

**Sibling**
- BUCY: 77%
- BUFLU: 76%

**Graft Failure**
- BUCY: 0
- BUFLU: 5

Andersson, B, BBMT 2008
Lee, JH, J Clin Oncol, 2012
Bu + FLU as a myeloablative CDT compared with BU + CY for AML in CR1 undergoing allo HSCT: a prospective and multicenter study

Liu, H, J of Hematology & Oncology, 2013
Randomized Study of 2 RIC Strategies for HLA-Matched, Related Allo PBSCT

Fluda-BU-ATG
- Fludarabin: 30 mg/m²
- Po Busulfan: 4 mg/kg
- Thymoglobulin: 2.5 mg/kg
- PBSC Transplant
- CSA: 3 mg/kg
- MMF: 2g/day (d1→d+28)

Fluda-TBI
- Fludarabin: 30 mg/m²
- TBI: 2 gy
- PBSC Transplant
- CSA: 3 mg/kg
- MMF: 2g/day (d1→d+28)

Flu-Bu-ATG | Flu-Bu-ATG | Flu-TBI
---|---|---
N=69 | N=70
Age | 54 (21-65) | 52 (34-65)
- AML/HMY | 37% | 27%
- HLY | 63% | 73%
- Advanced | 63% | 65%

2-4 aGVHD | 47% | 28%
Ext cGVHD | 61% | 46%
NRM | 38% | 22%
Relapse | 27% | 54%

Blaise, D, cancer 2012
Reduced toxicity approach
Does GVHD remain the same old challenge?

Non Relapse Mortality

Relapse

p=0.003

p=0.005

0: No GVHD; 1: Mild; 2: Moderate; 3: Severe

Saillard, C, Submitted
Mechanisms of action of antithymocyte globulin: T-cell depletion and beyond

- The polyclonal nature of Thymoglobuline is reflected in its diverse effects on the immune system:
  - T-cell depletion in blood and peripheral lymphoid tissues
  - Interference with leukocyte/endothelium interactions
  - Apoptosis in all B-cell lineages
  - Induction of Tregs / NKT cells

- Thymoglobuline provides multifaceted immunomodulation
GVHD prophylaxis with ATG: Which is more important, dose or timing?

- 257 adults with MUD or Haplo HSCT
- Age: 32 (15-64)
- CR1 + CR2: 66%
- CY-TBI: 56%

<table>
<thead>
<tr>
<th>DOSE (mg/kg)</th>
<th>TIMING</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>day -3</td>
</tr>
<tr>
<td>7.5</td>
<td>day -2</td>
</tr>
<tr>
<td>11.25</td>
<td>day -1</td>
</tr>
<tr>
<td>15</td>
<td>day +1</td>
</tr>
<tr>
<td></td>
<td>day +7</td>
</tr>
</tbody>
</table>

Sormani, EBMT, 2007
Courtesy from A Bacigalupo
GVHD prophylaxis with ATG: which is more important, dose or timing?

**MV analysis: Timing**

Sormani, EBMT, 2007

*Courtesy from A Bacigalupo*
**Patient Age**
- Age ≥ 55
  - 23

**Comorbidity Score >2**
- 21

**DIAGNOSIS**
- Acute Leukemia
  - 39
- Myeloid Malignancies
  - 16
- Lymphoid Malignancies
  - 45

**DISEASE STATUS**
- CR1/CP1
  - 45
- CR>1 or RP/Stable
  - 39
- Refractory
  - 14

Blaise, D, Exp Hematol, 2010
rATG: 2.5 vs. 5 mg/kg
Retrospective study on 229 patients

<table>
<thead>
<tr>
<th></th>
<th>day-5</th>
<th>day -4</th>
<th>day -3</th>
<th>day -2</th>
<th>day -1</th>
<th>day 0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fludarabine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>A</td>
</tr>
<tr>
<td>Busulfan</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>A</td>
</tr>
<tr>
<td>r ATG 2.5 mg/kg/d</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>A</td>
</tr>
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</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>day-5</th>
<th>day -4</th>
<th>day -3</th>
<th>day -2</th>
<th>day -1</th>
<th>day 0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fludarabine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>A</td>
</tr>
<tr>
<td>Busulfan</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>A</td>
</tr>
<tr>
<td>r ATG 2.5 mg/kg/d</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>A</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>
### Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>1-day ATG: 2.5 mg/kg</th>
<th>2-day ATG 5 mg/kg</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Follow-up</strong></td>
<td>62 [10-108]</td>
<td>16 [2.5-55]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>51 [18-70]</td>
<td>58 [24-68]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Myeloid Malignancies</td>
<td>56%</td>
<td>49%</td>
<td>0.3497</td>
</tr>
<tr>
<td>Kahl classification</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>19%</td>
<td>23%</td>
<td>0.6309</td>
</tr>
<tr>
<td>Standard</td>
<td>57%</td>
<td>51%</td>
<td></td>
</tr>
<tr>
<td>high</td>
<td>24%</td>
<td>26%</td>
<td></td>
</tr>
<tr>
<td>IV Busulfan</td>
<td>5%</td>
<td>98%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Unrelated Donor</td>
<td>2%</td>
<td>38%</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*Crocchiolo, R, Cancer, 2013*
Graft vs. Host Disease

Grade 3-4 Acute GvHD

HR (95% CI) = 0.26 (0.10 – 0.69), p=0.007

Extensive cGvHD

HR (95% CI) = 0.235 (0.12 – 0.48), P<0.0001

Crocchiolo, R, Cancer, 2013
AML/MDS patients after MRD HSCT

<table>
<thead>
<tr>
<th>Variable</th>
<th>1-day ATG (N=53)</th>
<th>2-day ATG (N=22)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>49 [18-70]</td>
<td>60 [31-68]</td>
<td>0.032</td>
</tr>
<tr>
<td>AML/MDS</td>
<td>89% / 11%</td>
<td>82% / 18%</td>
<td>0.325</td>
</tr>
<tr>
<td>High Risk Disease*</td>
<td>40%</td>
<td>45%</td>
<td>0.415</td>
</tr>
<tr>
<td>CsA/CsA+MMF</td>
<td>81% / 19%</td>
<td>100% / 0</td>
<td>0.024</td>
</tr>
</tbody>
</table>

- *High risk AML: secondary AML, Adverse caryotype, no CR at the time of transplantation
- *High risk MDS: high risk IPSS, therapy related MDS

Devillier, R, BMT 2012
The increase from 2.5 to 5 mg/kg of r-ATG dose in RIC reduces acute and chronic GVHD after allo MRD HSCT

Devillier, R, BMT 2012
Impact of immune modulation with anti-T-cell antibodies on the outcome of reduced-intensity allogeneic hematopoietic stem cell transplantation for hematologic malignancies

The median total dose of alemtuzumab was 60 mg. Among patients who received ATG, approximately 70% of recipients received rabbit ATG (median dose, 7 mg/kg) and 27%, horse ATG (median dose, 40 mg/kg). The type of ATG administered was not reported for 3% of patients.
Importance of Dose?

GVHD: High
NRM: High

OPTIMAL WINDOW?

GVHD: Low
Infections: high
NRM: High
Relapses: High

R-ATG dose

2.5
5
>7

mg/kg

Survival

Blaise, Exp Hematol, 2010
Devillier, R, BMT, 2012
Crocchiolo, R, Cancer, 2013

Duggan, P, BMT, 2002
Hamadani, BBMT, 2009
Malard, BBMT, 2011
Devillier, R, BMT, 2012
Siddiqi, Hematology, 2012
Crocchiolo, R, Cancer, 2013

Faucher, exp Hematol, 2003
Mohty, Blood, 2003
Mohty, Leukemia, 2003
Hamadani, BBMT, 2009
Soiffer, Blood, 2011
Blaise, Exp Hematol, 2010
Devillier, R, BMT, 2012
Crocchiolo, R, Cancer, 2013

Duggan, P, BMT, 2002
Hamadani, BBMT, 2009
Malard, BBMT, 2011
Devillier, R, BMT, 2012
Siddiqi, Hematology, 2012
Crocchiolo, R, Cancer, 2013

Faucher, exp Hematol, 2003
Mohty, Blood, 2003
Mohty, Leukemia, 2003
Hamadani, BBMT, 2009
Soiffer, Blood, 2011
What about timing?
Protective Conditioning for AGVHD

ATG 1.5 mg/kg/day
Days−11 to −7
Days−11 to −7 Days−4 to −1
TLI 800 cGy over 10 fractions

CSA
Day 0
MMF
Day 180

ANC
ALC

Absolute Count x10³/mm³

Before conditioning Day 0 3 mo 6 mo 9 mo 12 mo

A

Cumulative Incidence of Non-Relapse Mortality

B

Cumulative Incidence of Non-Relapse Mortality

Lowsky, NEJM, 2005
Kohrt, Blood, 2009
Multicenter Experience using TLI and ATG as conditioning for allografting in hematological malignancies

**Graph A:**
- X-axis: Months post transplant
- Y-axis: Number of Patients
- Events: 0, 0, 2, 3, 5
- Patients: 45, 45, 40, 36, 34
- Curves:
  - Death without acute GvHD
  - Acute grade II-IV GvHD

**Graph B:**
- X-axis: Months post transplant
- Y-axis: Number of Patients
- Events:
  - Chronic GvHD: 41, 33, 24, 22, 18, 10, 8
  - Death without chronic GvHD

*Biol Blood Marrow Transplant 18:1600-1613, 2012*
The addition of one-day rest between last ATG infusion and stem cell infusion did not affect GVHD occurrence after allogeneic transplantation with fludarabine-busulfan-ATG conditioning.

<table>
<thead>
<tr>
<th></th>
<th>No rest</th>
<th>1-day ATG rest</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>N. patients</td>
<td>57</td>
<td>51</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>57 (21-68)</td>
<td>58 (20-71)</td>
<td>0.27</td>
</tr>
<tr>
<td>Donor: sibling/MUD/MMUD</td>
<td>36/14/7</td>
<td>23/19/9</td>
<td>0.17</td>
</tr>
<tr>
<td>Disease risk* : low/interm/high/very high</td>
<td>3/41/10/2 **</td>
<td>3/34/13/1</td>
<td>0.77</td>
</tr>
</tbody>
</table>
**THE ADDITION OF ONE-DAY REST BETWEEN LAST ATG INFUSION AND STEM CELL INFUSION DID NOT AFFECT GVHD OCCURRENCE AFTER ALLOGENEIC TRANSPLANTATION WITH FLUDARABINE-BUSULFAN-ATG CONDITIONING**

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<td>0.77</td>
</tr>
<tr>
<td>Incidence at 2-y=</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 2-4 aGvHD</td>
<td>23% (12-34)</td>
<td>24% (12-36)</td>
<td>0.73</td>
</tr>
<tr>
<td>Grade 3-4 aGvHD</td>
<td>11% (3-19)</td>
<td>4% (0-9)</td>
<td>0.23</td>
</tr>
<tr>
<td>cGvHD overall</td>
<td>35% (22-48)</td>
<td>39% (24-54)</td>
<td>0.52</td>
</tr>
<tr>
<td>cGvHD extensive</td>
<td>26% (14-38)</td>
<td>20% (8-32)</td>
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The addition of one-day rest between last ATG infusion and stem cell infusion did not affect GVHD occurrence after allogeneic transplantation with fludarabine-busulfan-ATG conditioning

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<th>No rest</th>
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<tr>
<td>N. patients</td>
<td>57</td>
<td>51</td>
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<td>Age</td>
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<td>Disease risk* : low/interm/high/very high</td>
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<td>Grade 2-4 aGvHD</td>
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<tr>
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<td>cGvHD extensive</td>
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<tr>
<td>OS (95%CI)</td>
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<tr>
<td>PFS (95%CI)</td>
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Conclusions

- rATG is efficient preventing severe forms of GVHD
- In the setting of minimal conditioning it prompts
  - Myeloid and lymphoid engraftment
  - GVHD prevention
- In the setting of RIC or MA-RTC
  - An intermediate dose
    - Triggers engraftment
    - Prevents GVHD
    - Is not associated with increased disease relapse
    - Is not associated with increased infection rates
  - Optimal timing? Yet to be determined
    - Caution if few hours before graft infusion
    - Allow tuning of Immunosuppression / T-cell depletion effects
    - Probable balance dose / timing
Reduced Toxicity Conditionings in older pts
NMAC vs. RIC vs. MA-RTC

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<tbody>
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</tr>
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<td>Age</td>
<td>60 (5-74)</td>
</tr>
<tr>
<td>AML</td>
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</tr>
<tr>
<td>CR1 / CR&gt;1 /adv</td>
<td>58% / 36% / 6%</td>
</tr>
<tr>
<td>CDT</td>
<td></td>
</tr>
<tr>
<td>TBI2</td>
<td>100%</td>
</tr>
<tr>
<td>BU2</td>
<td></td>
</tr>
<tr>
<td>BU4</td>
<td></td>
</tr>
<tr>
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<td>Rabbit ATG</td>
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<td>MRD / UD</td>
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Reduced Toxicity Conditionings in older pts
NMAC vs. RIC vs. MA-RTC

CR1 AML

NMAC
N=160

RIC
N=78

MA-RTC
N= 25
Fifteen years of RTC…So?

- **Achievements in transplantation**
  - Stable engraftment
  - Decreased NRM
  - There is an efficient allogeneic antitumor effect

- **Achievements in therapy**
  - Older and/or unfit patients
  - Different diagnoses
  - Alternative donors: Haploidentical Donor

Thus…RTC (RIC/MA-RTC) have changed the stage!
What’s next?
Remaining major issues

- **Tumor control**
  - Are MA-RTC a step forward?
    - *Dose Intensity studies*
  - Optimal Immunosuppression?
    - *Ex vivo T Cell depletion vs. No?*
  - Post Transplant intervention?
    - Cellular immunotherapy
    - Tumor antigen vaccination
    - Targeted therapy

- **Quality of life**
  - Efficiency must be evaluated on composite events:
    - Tumor control + survival + quality of survival
Acknowledgments

- **Institut Paoli Calmettes**
  - **Transplant Program**
    - S Furst
    - J El Cheikh
    - L Castagna
    - A Granata
    - S Harbi
    - R Crocchiolo
    - R Devillier
    - C Oudin
    - C Saillard
    - I Rahal
  - **Nursing Staff**
    - L Caymaris
  - **Cellular Therapy Unit**
    - C Chabannon
  - **Hematology department**
    - N Vey
    - R Bouabdallah
  - M Mothy (Nantes, Paris)
  - FB Petersen (SLC)
  - B Andersson (Houston)

R. Devillier  R. Crocchiolo  C Saillard  I Rahal
That's all Folks!