CONTROVERSIE NEL TRAPIANTO DI CELLULE STAMINALI EMOPOIETICHE

RUOLO DEL SECONDO TRAPIANTO NELLA LEUCEMIA ACUTA MIELOIDE IN RECIDIVA

Alida Dominietto

CORSO EDUCAZIONALE GITMO
BARI, 6 – 7 Giugno 2017
• Allogeneic hematopoietic stem cell transplantation (HSCT) is the treatment of choice for patients with acute leukemia.

• During the last 15 years transplant related mortality (TRM) has been significantly reduced due to better supportive care, improving in HLA-typing, prophylaxis and treatment of infections and the introduction of reduced intensity conditioning regimens.

• On the contrary relapse related death (RRD) has remained unchanged over the past 3 decades.
Van den Brink, BBMT, 2010
• Treatment options for relapsed patients after allogeneic HSCT included:
  
  • DLI
  • Chemotherapy with/without DLI
  • Novel drugs with/without DLI
  • Second allogeneic transplantation
SECOND ALLOGENEIC STEM CELL TRANSPLANTATION FOR ACUTE AND CHRONIC LEUKEMIA
- A Prognostic Factor Analysis -

International Bone Marrow Transplant Registry

Eapen et al. Bone Marrow Transplant 2004;34:721-727

Autologous Blood and Marrow Transplant Registry

N=279 pts
INCLUSION AND EXCLUSION CRITERIA

- **Inclusion criteria**
  - ALL, AML and CML
  - HLA-identical sibling donor for 1\textsuperscript{st} and 2\textsuperscript{nd} SCT
  - 2\textsuperscript{nd} SCT between 1990-2000

- **Exclusion criteria**
  - Recipients of alternative donor 2\textsuperscript{nd} SCT
  - Recipients of donor leukocyte infusion
  - Recipients of non-myeloablative SCT
CUMULATIVE INCIDENCE OF TRM AND RELAPSE AFTER 2ND TRANSPLANTATION

CUMULATIVE INCIDENCE, %

YEARS

Persistent or recurrent leukemia 42%

TRM

26%

30%
PROBABILITY OF LFS AND OVERALL SURVIVAL AFTER 2ND TRANSPLANTATION

CUMULATIVE INCIDENCE, %

Y YEARS

Overall Survival

LFS

41%

38%

28%

28%
Figure 3  Probability of overall survival after second transplantation. (A) Age $\leq 20$ years, duration of remission $> 6$ months; (B) age $> 20$ years, duration of remission $> 6$ months; (C) age $\leq 20$ years, duration of remission $\leq 6$ months; and (D) age $> 20$ years, duration of remission $\leq 6$ months.
124 consecutive patients received a second transplant from October 1985 to July 2010, after prior allogeneic (n=60) or autologous (n=64) HSCT.
<table>
<thead>
<tr>
<th></th>
<th>N (%)</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;20</td>
<td>4 (3.2)</td>
<td>0</td>
</tr>
<tr>
<td>20-40</td>
<td>62 (50.0)</td>
<td>1</td>
</tr>
<tr>
<td>&gt;40</td>
<td>58 (46.8)</td>
<td>2</td>
</tr>
<tr>
<td><strong>Disease stage</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early</td>
<td>9 (7.3%)</td>
<td>0</td>
</tr>
<tr>
<td>Intermediate</td>
<td>53 (42.3%)</td>
<td>1</td>
</tr>
<tr>
<td>Advanced</td>
<td>62 (50.0)</td>
<td>2</td>
</tr>
<tr>
<td><strong>Duration of disease</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-second SCT (months)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;12</td>
<td>9 (7.3)</td>
<td>0</td>
</tr>
<tr>
<td>&gt;12</td>
<td>115 (92.7)</td>
<td>1</td>
</tr>
<tr>
<td><strong>Donor match</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HLA-id.sib.</td>
<td>75 (60.5)</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
<td>49 (39.5)</td>
<td>1</td>
</tr>
<tr>
<td><strong>Patient/donor gender</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M/F</td>
<td>22 (17.7)</td>
<td>1</td>
</tr>
<tr>
<td>Other</td>
<td>100 (82.3)</td>
<td>0</td>
</tr>
</tbody>
</table>

**Table 2. EBMT Risk Score at Second SCT (A)**

**SCORE: 0 - - - - >7**
NRM and OS according to the EBMT RISK SCORE at SECOND TRANSPLANT

<table>
<thead>
<tr>
<th>EBMT Score at Second SCT</th>
<th>Probability of NRM at 1 Year (95% CI)</th>
<th>Probability of Survival at 5 Years (95% CI)</th>
<th>P Value</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-3</td>
<td>25 (20.2)</td>
<td>28.0 (15-53)</td>
<td>.0003</td>
<td>.0003</td>
</tr>
<tr>
<td>4</td>
<td>40 (32.3)</td>
<td>33.2 (21-52)</td>
<td></td>
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</tr>
<tr>
<td>&gt;4</td>
<td>57 (46.0)</td>
<td>58.8 (47-73)</td>
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</tbody>
</table>

SCT indicates stem cell transplantation; CI, confidence interval; EBMT, European blood and marrow transplant; NRM, nonrelapse mortality.

Rezvani, BBMT 2011
# Predicting Factors of Survival in Multivariable Analysis

<table>
<thead>
<tr>
<th></th>
<th>RR</th>
<th>P</th>
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<tbody>
<tr>
<td>High Score</td>
<td>2.83</td>
<td>0.001</td>
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<tr>
<td>Inter Score</td>
<td>1.75</td>
<td>0.09</td>
</tr>
<tr>
<td>Int 1(^{st}) TX -&gt; 2(^{nd}) TX ( &lt; 20 months )</td>
<td>1.59</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Rezvani, BBMT 2011
OS according to RISK SCORE and INTERVAL TRANSPLANT

5YY OS 48% VS 9% , P=0.00006

Rezvani, BBMT 2011
ORIGINAL ARTICLE
Long-term outcome and prognostic factors of second allogeneic hematopoietic stem cell transplant for acute leukemia in patients with a median follow-up of ≥ 10 years

G Andreola¹, M Labopin², D Beelen³, P Chevallier⁴, R Tabrizi⁵, A Bosi⁶, M Michallet⁷, S Santarone⁸, G Ehringer⁹, E Polge², D Laszlo¹, C Schmid¹⁰,¹², A Nagler¹¹ and M Mohty²,¹²

n= 286        AML = 166        ALL = 120
MAC
YY of TX 1985 – 2000
Median FUP 11.3 yy

EBMT registry
10 yy OS according to RISK SCORE

- NO CR
- NO TBI
- 1°SCT-relapse < 10 mo

Andreola, BMT 2015
• Studio retrospettivo all’interno del GITMO
• Promotore FA-R.I.T.M.O nel 2012
• 40 centri (adulti e pediatrici)
• YY TX 2006-2011
• 208 pazienti
• AML (n=138) e ALL (70)
• OS obiettivo primario
<table>
<thead>
<tr>
<th>CIC</th>
<th>ADESIONE</th>
<th>INVIATO I DATI</th>
</tr>
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<tbody>
<tr>
<td>141</td>
<td>BRESCIA</td>
<td>SI</td>
</tr>
<tr>
<td>217</td>
<td>GENOVA</td>
<td>SI</td>
</tr>
<tr>
<td>232</td>
<td>ROMA</td>
<td>SI</td>
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<tr>
<td>240</td>
<td>BOLOGNA</td>
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<td>248</td>
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<tr>
<td>274</td>
<td>GENOVA</td>
<td>SI</td>
</tr>
<tr>
<td>286</td>
<td>PAVIA</td>
<td>SI</td>
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<tr>
<td>304</td>
<td>FIRENZE</td>
<td>SI</td>
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<tr>
<td>307</td>
<td>ROMA</td>
<td>SI</td>
</tr>
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<td>526</td>
<td>SG ROTONDO</td>
<td>SI</td>
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<tr>
<td>606</td>
<td>CUNEO</td>
<td>SI</td>
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<tr>
<td>658</td>
<td>BERGAMO</td>
<td>SI</td>
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<tr>
<td>788</td>
<td>ANCONA</td>
<td>SI</td>
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<tr>
<td>790</td>
<td>BOLOGNA</td>
<td>SI</td>
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<td>792</td>
<td>CATANIA</td>
<td>SI</td>
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<td>813</td>
<td>MILANO</td>
<td>SI</td>
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<tr>
<td>299</td>
<td>BOLZANO</td>
<td>SI</td>
</tr>
<tr>
<td>649</td>
<td>BARI</td>
<td>SI</td>
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<tr>
<td>766</td>
<td>NAPOLI</td>
<td>SI</td>
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<tr>
<td>231</td>
<td>TORINO</td>
<td>SI</td>
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<tr>
<td>285</td>
<td>PADOVA</td>
<td>SI</td>
</tr>
<tr>
<td>557</td>
<td>PAVIA</td>
<td>SI</td>
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<tr>
<td>692</td>
<td>PALERMO</td>
<td>SI</td>
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<tr>
<td>756</td>
<td>ROMA</td>
<td>SI</td>
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<tr>
<td>791</td>
<td>CAGLIARI</td>
<td>SI</td>
</tr>
<tr>
<td>705</td>
<td>UDINE</td>
<td>SI</td>
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ADESIONI 26 CENTRI
INVIO DATI 16 CENTRI
Emendamento al protocollo nel 2013


Informazioni aggiuntive:
DLI e/o CHT+DLI pre e post II TX
GVHD a/c grado massimo/timing
Stesso donatore o diverso
Condizionamento RIC/MAC
Stop IS post II TX
DLI profilattiche post II TX
Criteri di inclusione/esclusione

Diagnosi  AML
            ALL
Recidiva di malattia dopo il trapianto di midollo osseo allogenico

Rigetto
Poor graft function
Chimerismo misto
Assenza di recidiva di malattia
Diagnosi diversa da AML e ALL
## PATIENTS CHARACTERISTICS (n=208)

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<thead>
<tr>
<th>DISEASE</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>AML</td>
<td>138</td>
<td>66</td>
</tr>
<tr>
<td>ALL</td>
<td>70</td>
<td>34</td>
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<table>
<thead>
<tr>
<th>DISEASE PHASE</th>
<th>n</th>
<th>%</th>
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</thead>
<tbody>
<tr>
<td>CR</td>
<td>59</td>
<td>28</td>
</tr>
<tr>
<td>No CR</td>
<td>149</td>
<td>72</td>
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</table>

<table>
<thead>
<tr>
<th>Sex mism</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>F→M</td>
<td>45</td>
<td>24</td>
</tr>
<tr>
<td>other</td>
<td>159</td>
<td>76</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age</th>
<th>40 (4-66) yy</th>
</tr>
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<table>
<thead>
<tr>
<th>Year of tx</th>
<th>2006-2012</th>
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<table>
<thead>
<tr>
<th>Int 1°-2°tx</th>
<th>377 (35-4719) dd</th>
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</thead>
<tbody>
<tr>
<td>Int 1°Tx - REL</td>
<td>236 (15-4553) dd</td>
</tr>
<tr>
<td>Int 1°REL -2°tx</td>
<td>103 (16-2167) dd</td>
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</table>

<table>
<thead>
<tr>
<th>Median FUP</th>
<th>250 (4-3794) dd</th>
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</table>
### Transplant Characteristics (1)

#### (n=208)

<table>
<thead>
<tr>
<th>Category</th>
<th>n</th>
<th>(%)</th>
</tr>
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<tbody>
<tr>
<td><strong>Donor Type</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SIB+FAM MISM</td>
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<td>37</td>
</tr>
<tr>
<td>ALT(MUD/MISM/HAPLO)</td>
<td>130</td>
<td>63</td>
</tr>
<tr>
<td><strong>Conditioning</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RIC</td>
<td>100</td>
<td>48</td>
</tr>
<tr>
<td>MA</td>
<td>108</td>
<td>51</td>
</tr>
<tr>
<td><strong>SC Source</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BM</td>
<td>54</td>
<td>26</td>
</tr>
<tr>
<td>PB</td>
<td>132</td>
<td>63</td>
</tr>
<tr>
<td>CB</td>
<td>22</td>
<td>11</td>
</tr>
<tr>
<td><strong>Donor AT 2°TX</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>YES</td>
<td>118</td>
<td>57</td>
</tr>
<tr>
<td>NO</td>
<td>90</td>
<td>43</td>
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<tr>
<td><strong>GvHD Proph</strong></td>
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<td></td>
</tr>
<tr>
<td>YES</td>
<td>190</td>
<td>91</td>
</tr>
<tr>
<td>NO</td>
<td>18</td>
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## TRANSPLANT CHARACTERISTICS (2)

### (n=208)

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<tr>
<th></th>
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<th>(%)</th>
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<tbody>
<tr>
<td>aGVHD</td>
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<tr>
<td>I-II</td>
<td>66</td>
<td>31</td>
</tr>
<tr>
<td>III</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>IV</td>
<td>9</td>
<td>4</td>
</tr>
<tr>
<td>cGVHD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LIM</td>
<td>24</td>
<td>11</td>
</tr>
<tr>
<td>EXT</td>
<td>40</td>
<td>19</td>
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<tr>
<td>STOP IS</td>
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</tr>
<tr>
<td>&lt;= d100</td>
<td>39</td>
<td>12</td>
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<td>101-180</td>
<td>33</td>
<td>19</td>
</tr>
<tr>
<td>&gt;180</td>
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<td>NO</td>
<td>26</td>
<td>12</td>
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<td>PROPH DLI</td>
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<tr>
<td>YES</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>w/o REL</td>
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<td>192</td>
<td>93</td>
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<td>11</td>
<td>5</td>
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<td>109</td>
<td>52</td>
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<tr>
<td>Alive/Dead</td>
<td>36</td>
<td>172</td>
</tr>
<tr>
<td>Dead for RELAPSE</td>
<td>110</td>
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</tr>
<tr>
<td>Dead for NRM</td>
<td>62</td>
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## Factors Predicting Overall Survival in Univariate Analysis (1)

<table>
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<tr>
<th></th>
<th>5yOS</th>
<th>p</th>
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<tbody>
<tr>
<td><strong>Disease phase</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>28%</td>
<td>0.03</td>
</tr>
<tr>
<td>No CR</td>
<td>9%</td>
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</tr>
<tr>
<td><strong>Donor type</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sib</td>
<td>22%</td>
<td></td>
</tr>
<tr>
<td>Alt</td>
<td>6%</td>
<td></td>
</tr>
<tr>
<td><strong>Recipient Age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;30yy</td>
<td>24%</td>
<td></td>
</tr>
<tr>
<td>&gt;30yy</td>
<td>21%</td>
<td></td>
</tr>
<tr>
<td><strong>Int. 1°-2°tx</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;365dd</td>
<td>10%</td>
<td></td>
</tr>
<tr>
<td>&gt;365dd</td>
<td>16%</td>
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<td><strong>Int. REL-2°tx</strong></td>
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<td>&lt;100dd</td>
<td>10%</td>
<td></td>
</tr>
<tr>
<td>&gt;100dd</td>
<td>15%</td>
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FACTORS PREDICTING OVERALL SURVIVAL IN UNIVARIATE ANALYSIS (2)

5yyOS  p

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<tr>
<th>SC source</th>
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<tbody>
<tr>
<td>BM</td>
<td>20%</td>
</tr>
<tr>
<td>PB</td>
<td>15%</td>
</tr>
<tr>
<td>CB</td>
<td>0%</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Sex mism</th>
<th>0.91</th>
</tr>
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<tr>
<td>F vs M</td>
<td>15%</td>
</tr>
<tr>
<td>other</td>
<td>12%</td>
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<table>
<thead>
<tr>
<th>Conditioning</th>
<th>0.66</th>
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<tbody>
<tr>
<td>RIC</td>
<td>14%</td>
</tr>
<tr>
<td>MA</td>
<td>14%</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Donor 2°tx</th>
<th>0.56</th>
</tr>
</thead>
<tbody>
<tr>
<td>=</td>
<td>18%</td>
</tr>
<tr>
<td>&lt;&gt;</td>
<td>11%</td>
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### NEGATIVE PREDICTORS OF OVERALL SURVIVAL IN MULTIVARIATE ANALYSIS

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Value</th>
<th>RR</th>
<th>P</th>
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<tr>
<td>Donor type</td>
<td>alternative</td>
<td>1.67</td>
<td>0.002</td>
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<tr>
<td>Recipient Age</td>
<td>&gt;=30yy</td>
<td>1.52</td>
<td>0.01</td>
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<tr>
<td>Int. 1°-2° TX</td>
<td>&lt;365dd</td>
<td>1.81</td>
<td>0.0001</td>
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<tr>
<td>Disease phase 2ndTx</td>
<td>no CR</td>
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NEGATIVE PREDICTORS OF RELAPSE AND NRM IN MULTIVARIATE ANALYSIS

<table>
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<th>Cox on relapse</th>
<th>RR</th>
<th>P</th>
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<tbody>
<tr>
<td>Recipient Age:</td>
<td>&gt;=30yy</td>
<td>1.44</td>
<td>0.07</td>
</tr>
<tr>
<td>Int. 1°-2° TX:</td>
<td>&lt;365dd</td>
<td>2.29</td>
<td>0.0001</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Cox on NRM</th>
<th>RR</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Source</td>
<td>CB</td>
<td>3.79</td>
</tr>
<tr>
<td></td>
<td>PB</td>
<td>1.3</td>
</tr>
</tbody>
</table>
RISK SCORE FOR OS AT SECOND TX

Donor type:  
sibling  0  
alternative  1

Recipient Age:  
<30yy  0  
>=30yy  1

Int. 1°-2° TX  
<365dd  1  
>=365dd  0

Disease phase:  
CR  0  
no CR  1

SCORE: 0 - - - - >4
GITMO data: 5 yy OS according to risk score

- A = score 0-1, n=28, 35%
- B = score 2, n=72, 23%
- C = score 3-4, n=108, 5%

p<0.001

% of OS vs. days from tx
NEGATIVE IMPACT OF CB AS STEM CELL SOURCE

Survival Plot

Survival days from tx

% of OS

A: BM n=54 20%
B: PB n=132 15%
C: CB n=22 0%

p=0.04

CR

p=0.2

A: BM n=23 30%
B: PB n=32 30%
C: CB n=4 0%

NO CR

p=0.03

A: BM n=31 13%
B: PB n=100 11%
C: CB n=18 0%
CHANGING DONOR AT 2°TX DOES NOT INFLUENCE THE OUTCOME

p=0.8

A: DON = n=90  18%
B: DON <> n=117  11%
CONCLUSIONS (1)

Patients with acute leukemia relapsed after allogeneic HSCT have a very poor prognosis.

A second allogeneic HSCT is a treatment option, but risk assessment should be evaluated.

Younger age (< =30 yy), interval time 1°2°Tx > 1 yy, hla-identical sibling, CR at the time of 2°Tx are the best predictors of outcome.
CONCLUSIONS(2)

Short interval time between 1° and 2° Tx is the most important negative predictor of outcome in multivariate analysis.

MA conditioning should be used for patients in remission at 2°TX to improve survival.

Changing donor at 2° Tx had no impact on the outcome.
<table>
<thead>
<tr>
<th>Centers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Milano San Raffaele</td>
</tr>
<tr>
<td>Genova - Ospedale San Martino</td>
</tr>
<tr>
<td>Torino Ospedale San Giovanni Battista</td>
</tr>
<tr>
<td>Pescara Ospedale Civile</td>
</tr>
<tr>
<td>Firenze AO Careggi</td>
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<tr>
<td>Ancona Ospedali Riuniti</td>
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<td>Bologna Policlinico Sant’Orsola</td>
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<td>Cuneo S. Croce</td>
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<td>Napoli Federico II</td>
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<td>Cagliari Businco</td>
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<td>Monza Osp San Gerardo</td>
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<tr>
<td>Catania Ferrarotto</td>
</tr>
<tr>
<td>Udine Policlinico Universitario</td>
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### NEGATIVE PREDICTORS OF SURVIVAL IN MULTIVARIATE ANALYSIS (first analysis)

<table>
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<th>Factor</th>
<th>Value</th>
<th>HR</th>
<th>P</th>
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<tr>
<td>Donor type</td>
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<td>0.005</td>
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<td>Disease phase 2ndTx</td>
<td>no CR</td>
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<td>0.014</td>
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<tr>
<td>Int. 1°-2° TX</td>
<td>&lt;365dd</td>
<td>1.46</td>
<td>0.011</td>
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<tr>
<td>Recipient Age</td>
<td>&gt;=30yy</td>
<td>1.40</td>
<td>0.025</td>
</tr>
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</table>
# RISK SCORE FOR OS AT SECOND TX

<table>
<thead>
<tr>
<th>Factor</th>
<th>Value</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recipient Age:</td>
<td>&lt;30yy</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>&gt;=30yy</td>
<td>1</td>
</tr>
<tr>
<td>Disease phase:</td>
<td>CR</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>no CR</td>
<td>1</td>
</tr>
<tr>
<td>Int. 1°-2° TX</td>
<td>&lt;365dd</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>&gt;=365dd</td>
<td>0</td>
</tr>
<tr>
<td>Donor type:</td>
<td>sibling</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>alternative</td>
<td>1</td>
</tr>
</tbody>
</table>

**SCORE:** 0 - - - - >4
GITMO data: 5 yy OS according to risk score

A = score 0-1, n=55, 35%
B = score 2, n=112, 23%
C = score 3-4, n=141, 17%

p < 0.001