Haploidentical stem cell transplantation: potential and future perspectives

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Hôpitaux Universitaires de Genève
Allogeneic HSCT – in Europe (related and unrelated, CB and haplo): 2014 EBMT

J Passweg et al.
BMT 2016
Importance of HLA matching for the Tx outcome (1)

- The survival rate depends on the HLA-matching
- HLA-mismatches reduce the survival rate by approx. 10% each

Petersdorf et al., Blood (2006)
Which donor of HSC?

Potential donor

- **family**: HLA-ident. 25% haplo-ident. >75%
- **Unrelated adult donor**: 10/10 matched ~ 50%
- **Cord blood**: 4-6/6 matched >75%
Segregation of HLA haplotypes

Donor in family – HLA are inherited haploidentical
How to increase the possibilities of alloHSCT without a matched donor?

- Early studies with haplo HSCT illustrate major issue of crossing the HLA barriers:
  - if donor T cells left → excessive GVHD associated with death
  - if Tdep of graft and not of recipient → excessive graft failure
  - if intense conditioning and Tdep → too many death of opportunistic infection

- need to obtain engraftment, control GVHD and have decreased incidence of infections while preserving immunity after haplo HSCT
Syngeneic (twin)

Mismatched donor

Matched unrelated donor

HLA-identical sibling

T-cell depletion

Increasing GvHD

Increasing Relapse
New concept allowing to transplant mismatched donor-patient: haplo-identical donor = a potential donor for everybody
Standard way of allo-HSCT

Donor
HLA-identical sibling or UD 9-10/10 or CB

PBSC or BM or CB

chemotherapy
radiotherapy

D0

graft

D1

IS post alloHSCT: CSA or tacrolimus D-1 à D+180
MAC: MTX D+1, D+3 et D+6 or
RIC: MMF D-3 à D+28
The Baltimore concept: mechanism of T cell depletion after post-transplant Cyclophosphamide (PT Cy)

Luznik et al. Semin Oncol. 2012; 39
Mechanism of cytotoxic action on proliferating cells

Sensitive cells such as tumor or T cells

Cytotoxic action on proliferating cells

Resistant cells such as hematopoietic stem cells

Cyclophosphamide (inactive)

Cytotoxic Resistance

ALDH ↘

Aldehyde dehydrogenase

Sensitive cells such as tumor or T cells

ALDH ↗

Alloreactive T cell

4-Hydroxycyclophosphamide

Aldophosphamide

Liver

Donor CD4⁺ Foxp3⁺ regulatory T cells are necessary for post-transplantation cyclophosphamide-mediated protection against GVHD in mice.

Sudipto Ganguly¹, Duncan B. Ross², Angela Panoskaltsis-Mortari³, Christopher G. Kanakry¹, Bruce R. Blazar³, Robert B. Levy², and Leo Luznik¹

Blood 2014;124:2131

$\text{T} \text{regs} \xrightarrow{\text{ALDH}} \text{Resistance to Cy} \xrightarrow{} \text{Regulation of GVHD}$
First attempt in haplo-HSCT with reduced intensity conditioning (RIC) and Cy post-BMT
RIC haplo-HSCT with CY post-transplant

- 67 pts advanced hem. malignancies
- SC source: bone marrow
  --median age of pts: 46 years
- Graft failure: 9 (13%) with 8 autologous recovery
- aGvHD grade II-IV : 36% III-IV:6%
- cGvHD: 5% (CY 2 days) -25% (CY 1 day)

Luznik L. et al. BBMT 2008:14;641
Then haplo-HSCT with myeloablative conditioning (MAC)

Bashey A. and Solomon SR. BMT 2014:49;999
MAC haplo-HSCT with CY post-transplant

- 30 pts advanced hem. malignancies
- SC source: PBSC
- median age: 46 years
- Graft failure: none
- aGvHD grade II-IV : 43% III-IV:23%
- cGvHD: 56%

Solomon SR. et al. BBMT 2015;21;1299
Comparison haplo with CY post-transplant vs MRD and MUD

- 35 RIC, 18 MAC
- SC source: 21 PBSC/32 BM
- Graft failure: 1
- aGvHD grade II-IV: MRD:27%, MUD:39%, haplo:39% p=ns
- cGvHD: MRD:54%, MUD:54%, haplo:38% p<0.05

Bashey A. et al. JCO 2013;31:1310
Comparison haplo with CY post-transplant vs MUD in AML

- pts advanced hem. malignancies:
  192 haplo (104 MAC/88 RIC)/1982 MUD
  (1245 MAC/747 RIC)

- SC source: BM haplo 82%, MUD 19%

- Graft failure: haplo 10% vs MUD 3%
  MAC p=0.02
  for RIC haplo 7% vs MUD 4%, p=0.24

Ciurea SO.. et al. Blood 2015;126:1033
RIC Haplo with CY post-transplant for elderly

- 271 pts advanced hem. malignancies, med age: 61 y (50-75 y.).
- SC source: BM
- Graft failure: 6%
- aGvHD grade II-IV: all pts: 33% but higher for >70 y: 52%, p=0.009
- cGvHD: all pts: 10%

Kasamon YL. et al. JCO 2015:33;3152
RIC Haplo with CY post-transplant in relapsed/refractory HL

- 90 pts relapsed/refractory HL, MRD n=38, MUD n=24, haplo n=28.
- median age 33 yrs
- Graft failure: 0%
- aGvHD grade II-IV: MRD: 50%, MUD: 50%, haplo: 43%, p=ns
- cGvHD: MRD:50%, MUD: 63%, haplo: 35% p>0.05

Burroughs LM. et al. BBMT 2008:14;1279
NMA haplo CY post-BMT for advanced lymphoma

Figure 2. OS and PFS. Two-year OS: 95% CI 58.8–84.0%; 2-year PFS: 95% CI 51.8–78.6%.

Castagna L et al. BMT 2014:49 1475
NMA haplo CY post-BMT for advanced lymphoma

### Table 3. Univariate analysis for PFS and OS

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>N (%)</th>
<th>2 year PFS (%)</th>
<th>P-value</th>
<th>2 year OS (%)</th>
<th>P-value</th>
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<tr>
<td>All</td>
<td>49 (100)</td>
<td>65.2</td>
<td>0.497</td>
<td>71.4</td>
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<tr>
<td>Age median 44 (19–68)</td>
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<td>&lt; 44</td>
<td>25 (51)</td>
<td>68.0</td>
<td>0.497</td>
<td>76.0</td>
<td>0.472</td>
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<tr>
<td>≥ 44</td>
<td>24 (49)</td>
<td>62.5</td>
<td>0.497</td>
<td>66.7</td>
<td>0.472</td>
</tr>
<tr>
<td>Gender</td>
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<td></td>
<td>0.474</td>
<td></td>
<td>0.517</td>
</tr>
<tr>
<td>Female</td>
<td>21 (43)</td>
<td>71.4</td>
<td>0.474</td>
<td>76.2</td>
<td>0.517</td>
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<tr>
<td>Male</td>
<td>28 (57)</td>
<td>60.7</td>
<td>0.474</td>
<td>67.9</td>
<td>0.517</td>
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<td>Histology</td>
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<tr>
<td>HL</td>
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<td>73.9</td>
<td>0.126</td>
<td>85.2</td>
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<td>NHL</td>
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<td>AB0 compatibility</td>
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<td>0.322</td>
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<tr>
<td>Comp</td>
<td>29 (59)</td>
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<td>0.852</td>
<td>75.9</td>
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<td>Other</td>
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<td>CMV serology (D/R)</td>
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<td>neg/neg pos/neg</td>
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<td>64.3</td>
<td>0.981</td>
<td>64.3</td>
<td>0.657</td>
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<tr>
<td>pos/pos neg/pos</td>
<td>35 (71)</td>
<td>65.6</td>
<td>0.981</td>
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<td>20 (41)</td>
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<td>0.614</td>
<td>64.3</td>
<td>0.478</td>
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<td>15 (31)</td>
<td>66.7</td>
<td>0.614</td>
<td>66.7</td>
<td>0.478</td>
</tr>
</tbody>
</table>

**Figure 3.** NRM after haploidentical transplantation.

2y NRM 16%
Haplo with ATG in AML vs id-sibling donor prospective study

- 450 pts AML, id-sib n=219, haplo: n=231.
- median age id-sib: 40 yrs vs haplo: 28 yrs
- Graft failure: 0%
- aGvHD grade II-IV : id-sib: 13%, haplo: 36%, p<0.001
- cGvHD: id-sib: 15%, haplo: 42% p<0.001

Wang Y. et al. Blood 2015:125;3956
Haplo with CY post-BMT vs CBT

- 150 pts hematol malignancies, CB n=81, haplo: n=69.
- median age id-sib:47 yrs vs haplo: 44 yrs p=ns
- Graft failure: CBT:10% vs haplo:6%
- aGvHD grade II-IV : CBT: 50%, haplo: 34%, p=0.08
- cGvHD: CBT:12%, haplo: 6% p=0.001
--2 yrs OS CBT 45% vs haplo 69% p=0.1
--2 yrs PFS CBT 36% vs haplo 65% p=0.01, RI CBT 38% vs haplo 18% p=0.03

El-Cheick J. et al.
Cancer 2015:121;1809
Sequential clofarabine followed by RIC haplo CY post-BMT for refractory/relapsed lymphoma

Figure 1. Treatment plan for sequential T-cell-replete haplo-HSCT (RIC) utilizing HD CY post transplantation. Time axis in days is shown as a solid line with arrows indicating treatment interventions (start and duration of cytodestruction, conditioning, transplantation, immunosuppression, G-CSF). Clo = clofarabine; Flu = fludarabine; HSCT = haematopoietic SCT; Mel = melphalan.

Zoellner A-K. et al. BMT 2015:50 679
Sequential clofarabine followed by RIC haplo CY post-BMT for refractory/relapsed lymphoma OS and PFS at 2 years 68.8% (95% CI 40.5-85.6%) and 50%, NRM 18.75% (95% CI 4.3-41.1%) 1 y

Figure 3. Outcome (PFS/OS) after sequential haplo HSCT in 16 patients with aggressive, non-remission NHL.
Haplo with CY post-BMT ↓ CI of cGvHD

C

HIDT vs MRDT Gray's test $P = .045$
HIDT vs MUDT Gray's test $P = .015$

D

HIDT vs MRDT Gray's test $P = .014$
HIDT vs MUDT Gray's test $P = .013$

E

HIDT vs MRDT Gray's test $P = .022$
HIDT vs MUDT Gray's test $P = .007$

Bashey A. BBMT 2015:22;125
Table 1. Landmark and comparative studies

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Size</th>
<th>Source</th>
<th>Disease</th>
<th>Condition</th>
<th>aGvHD (2-3)</th>
<th>aGvHD (3-4)</th>
<th>cGvHD</th>
<th>Engrafted</th>
<th>OS (year)</th>
<th>NRM (year)</th>
<th>Relapse (year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Luznik et al.</td>
<td>2008</td>
<td>68</td>
<td>BM</td>
<td>All</td>
<td>RIC</td>
<td>34%</td>
<td>6%</td>
<td>13%</td>
<td>87%</td>
<td>36% (2)</td>
<td>15% (1)</td>
<td>51% (1)</td>
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<tr>
<td>Brunstein et al.</td>
<td>2011</td>
<td>50</td>
<td>BM</td>
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<td>RIC</td>
<td>32%</td>
<td>0%</td>
<td>13%</td>
<td>98%</td>
<td>62% (1)</td>
<td>7% (1)</td>
<td>45% (1)</td>
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<tr>
<td>Grosso et al.</td>
<td>2011</td>
<td>27</td>
<td>PBSC</td>
<td>All</td>
<td>MA</td>
<td>64%</td>
<td>8%</td>
<td>16%</td>
<td>92%</td>
<td>54% (1)</td>
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<td>Solomon et al.</td>
<td>2012</td>
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<td>All</td>
<td>MA</td>
<td>30%</td>
<td>10%</td>
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<td>Ciurea et al.</td>
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<td>MA</td>
<td>20%</td>
<td>5%</td>
<td>7%</td>
<td>94%</td>
<td>64% (1)</td>
<td>16% (1)</td>
<td>50% (1)</td>
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<td>Bashey et al.</td>
<td>2013</td>
<td>53</td>
<td>All</td>
<td>All</td>
<td>MA</td>
<td>30%</td>
<td>11%</td>
<td>38%</td>
<td>98%</td>
<td>64% (2)</td>
<td>7% (2)</td>
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<td>Raiola et al.</td>
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<td>BM</td>
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<td>All</td>
<td>14%</td>
<td>4%</td>
<td>15%</td>
<td>99%</td>
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<td>Castagna et al.</td>
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<td>69</td>
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<td>All</td>
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<td>90%</td>
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<td>0%</td>
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<td>97%</td>
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<td>Raj et al.</td>
<td>2014</td>
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<td>RIC</td>
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<td>87%</td>
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<td>AML</td>
<td>All</td>
<td>18%</td>
<td>5%</td>
<td>32%</td>
<td>91%</td>
<td>45% (3)</td>
<td>9% (3)</td>
<td>46% (1)</td>
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<tr>
<td>Solomon et al.</td>
<td>2015</td>
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<td>PBSC</td>
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<td>43%</td>
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<td>56%</td>
<td>100%</td>
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<tr>
<td>Kasamon et al.</td>
<td>2015</td>
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<td>BM</td>
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<td>32%</td>
<td>3%</td>
<td>10%</td>
<td>94%</td>
<td>46% (3)</td>
<td>12% (1)</td>
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<td>Blaise et al.</td>
<td>2016</td>
<td>31</td>
<td>All</td>
<td>All</td>
<td>All</td>
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<td>10%</td>
<td>13%</td>
<td>97%</td>
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<td>Kanate et al.</td>
<td>2015</td>
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<td>98%</td>
<td>60% (3)</td>
<td>17% (3)</td>
<td>36% (3)</td>
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</tbody>
</table>

Abbreviations: aGvHD = acute GvHD; BM = bone marrow; cGvHD = chronic GvHD; MA = myeloablative; MDS = myelodysplastic syndrome; NMA = non-myeloablative; NRM = non-relapse mortality; OS = overall survival; PBSC = peripheral blood stem cells; RIC = reduced intensity conditioning. RIC includes both RIC and NMA patients. Studies including >95% of grafts from either BM or PBSC were considered homogenous.
83 pts AML, MD: n=21, haplo: n=62.
- median age MD: 64 yrs vs haplo: 54 yrs p=0.012
- Graft failure: MD: 0 vs haplo: 1
RIC with CY post-BMT haplo vs MMUD donor

Abbreviations: 9/10 MUD, HLA-mismatched unrelated donor; aGVHD, acute graft-versus-host disease; ANC, absolute neutrophil count; cGVHD, chronic graft-versus-host disease; CI, confidence interval; CMV, cytomegalovirus; NRM, nonrelapse mortality; OS, overall survival; PFS, progression-free survival.

Gaballa S. et al.
Cancer 2016 online
CY post-BMT haplo for nonmalignant diseases

Figure 2. EFS and OS of 31 thalassemia patients undergoing haploidentical hematopoietic stem cell transplantation (haplo-SCT).

Anurathapan U. et al.
BMT 2016;51:813
Characteristics and Outcome of the 27 haplo-transplants at HUG

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Number</th>
<th>Percent</th>
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<td>Sex (M/F)</td>
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<td>Alive</td>
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</table>
OS of the 27 haplo-transplants at HUG

2 yrs OS=74% (64-84%)
Take home message

- Haplo-BMT with CY post-transplant (PTCy) is as safe and effective as HLA-matched sib BMT and MUD
- PTCy nullifies the (previously) detrimental impact of HLA mismatch on outcome
- It is possible to transplant elderly patients with this strategy (up to 75 years)
- Haplo-BMT with PTCy is sufficiently safe to be applied to treat non-malignant hematologic disorders
- ↓ CI of cGvHD with PTCy which may improve the quality of life of alloHSCT patients.
- In the end with all the sources of SC and haplo-BMT with PTCy virtually every patient can have a donor and have the chance being cured
Aknowledgements

Jean-Marie Tiercy
Marie-Thérèse Rubio

Thank you for your attention