Current Status of Haploidentical Hematopoietic Stem Cell Transplantation

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Hematopoietic SCT in Europe: data and trends in 2014

No. of HaploSCT are constantly increasing: 15.6% of alloSCT are mismatched related; overall 2,456 Haplo SCT (Adults-1,957; Pediatrics – 499)

25% increase in HaploSCT in 2014 vs to 2013

- 40,829 SCT; 15,765 alloSCT (43%); 20,704 autoSCT (57%)
- Compared to 2013 – 13% increase in alloSCT for AML CR1
- Main indication for SCT is Leukemias: 11,853 (33% of total, 96% allo)

*Passweg JR et al, BMT 2015*
Haploidentical Transplants
Platforms

• T cell depletion (Perugia experience)
  – Infusion of mega-dose CD34 (>10 \times 10^6/kg)
  – Absence of GVHD
  – Low relapse rates (NK –KIR alloreactivity)
  – High TRM – attributed to slow immune reconstitution

• New strategies with depletion of \(\alpha\beta+T\) and B+ cells (Germany-Italy)
NON T CELL DEPLETED HAPLO
Haploidentical Transplants Platforms

- **Non T cell depleted**
  - John Hopkins approach
    RIC or MAC BM with post CY
  - Chinese approach / Italian approach
    Mobilized bone marrow with high number of IST drugs (TBF- Primed BM- ATG + MTX + CSA +MMF +Basiliximab)
  - Modified Hopkins approach
    TBF or FluTBI- BM+ CSA + MMF+CTX (+3, +5)
    TreoFlu- PBSC-ATG+MMF+Rapamycin+CTX
HLA-Haploidentical Bone Marrow Transplantation for Hematologic Malignancies Using Nonmyeloablative Conditioning and High-Dose, Posttransplantation Cyclophosphamide

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Bone Marrow Infusion

Cyclophosphamide (Cy)
14.5 mg/kg/day

BMT
Day -6

Fludarabine 30 mg/m²/day

Day -5

TBI 200 cGy

Day -4

G-CSF

Day -3

MMF

Day -2

Day -1

Day 0

Cy 50 mg/kg/day,
day 3 (n=28) or
days 3,4 (n=40)

Tacrolimus

Day 5

Day 10

Day 20

Day 30

Day 40

Day 90

Day 180
Selective allodepletion with PT/Cy

Kanakry, et al. Sci Transl Med 2013,

Lymphs show heterogeneous ALDH1 expression
Most T cells, esp. those proliferating, express low levels of ALDH1 and are sensitive to Cy
Memory T cells, like other 'stem'-like cells, express high levels and are resistant to Cy
Increasing HLA mismatch $\rightarrow$ 
**Improved EFS without ↑GVHD**

Conclusion: It is not necessary to select the donor with the minimum HLA mismatch to the recipient.

Kasamon, BBMT 16: 482-489, 2010
Stem cell source in Haplo-SCT
Stem cell source in Haplo-SCT

- Since the early 2000s, BM was the stem cell source commonly reported in the non TCD haplo
- PBSC is more frequently used in single center, with a reported incidence of aGVHD ranging from 30%-40%
- Registry based study reports a higher incidence of grade II-IV aGVHD with no difference in cGVHD, NRM, relapse, LFS for PBSC compared to BM
BM or PBSC in RIC-Haplo

• 86 patients transplanted for hematological malignancies
• Hopkins regimen with fludarabine 150 mg/m², cyclophosphamide 29 mg/kg and 200cGy TBI
• GvHD prophylaxis: PT-Cy 50 mg/kg days +3 and +4 plus tacrolimus (target level 5-10 ng/mL) or CSA (target level 150-300 ng/mL) and MMF

O’Donnell et al, BMT 2016
BM or PBSC in RIC-Haplo

• No significant difference in the rate or global severity of grade II-IV aGvHD (33% and 40%, p=0.50) and chronic GvHD after haplo-BM or haplo-PB transplantation (21% and 14%, p=0.39)
• No difference in NRM
• Lower relapse (49% vs 20% at 1 year) after PB
• Comparable overall survival after transplantation of haplo-BM and haplo-PB

O’Donnell et al, BMT 2016
Immune recovery and early complication after Haplo-SCT
Immune recovery and early complication after Haplo-SCT

- T cell deficiency after HSCT remains an issue 1-2 years post-transplant, this will cause increase in risk of infectious complications, especially viral and fungal infections, as well as risk of relapse of disease

- It has been shown that recovery of T cell function in younger patients is faster than in older patients; this was probably a result of thymic dysfunction in aging population
Immune recovery and early complication after Haplo-SCT

- Other factors associated with thymic dysfunction include: conditioning (i.e. chemotherapy, TBI and the use of antibodies) and GvHD

- In Haplo SCT, regardless the type of conditioning regimen or the stem cell source used, viral infections range from 40% to 70%, in single center studies

Divide Bartolomeo, Blood 2013; Raiola BBMT 2013
Grade II-IV acute GVHD was not associated with HC (p=0.62). The occurrence of HC did not impact on OS (p=0.29).
Conclusion

- CD4+ and CD8+ T-cell early recovery is delayed after Haplo using ATG or PTCy

- Depletion of Ki-67+ effector/memory cells by PTCy may deplete some pathogen-specific clones and increase the risk of post-transplant infectious complications

- Strategies to spare non-alloreactive donor naïve and memory T cells, both to guarantee primary responses to newly encountered antigens and to confer adoptive immunity to Haplo recipient are needed
Comparison of outcomes after haplo and matched related or unrelated donor stem cell transplantation
T-Cell–Replete HLA-Haploidentical Hematopoietic Transplantation for Hematologic Malignancies Using Post-Transplantation Cyclophosphamide Results in Outcomes Equivalent to Those of Contemporaneous HLA-Matched Related and Unrelated Donor Transplantation

Asad Bashey, Xu Zhang, Connie A. Sizemore, Karen Manion, Stacey Brown, H. Kent Holland, Lawrence E. Morris, and Scott R. Solomon

J Clin Oncol 2013, 31:1310-1316
N=305: 90 MSD-116, UD (33 were 9/10)-99, Haplo

BuCy Cimustine AraC based regimen + ATG CSA, MMF and MTX for Haplo
N=459: 176 MSD- 86, UD (43 were 9/10)- 105, CBT - 92, Haplo

TBF or BuCy as MAC regimen, low dose TBI for RIC + CSA, MMF and ptCy for Haplo

Low incidence of acute and cGVHD for Haplo and UCBT recipients

Figure 4. Actuarial survival of patients stratified for donor type. Overall there is no statistically significant difference in survival.
Survival after Haplo-identical Related Compared with Matched Unrelated Donor Transplantation for Acute Myeloid Leukemia


Included are 2174 patients with AML aged 21-70 years and transplanted between 2009 and 2012. Cox regression models were built for recipients of myeloablative conditioning (MAC) (N=1245 MUD compared with N=104 haplo-identical) and reduced intensity conditioning (RIC) (N=737 MUD compared with 88 haplo-identical) transplants. Primary endpoint was 2-year overall survival.

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Transplant Conditioning Regimen Intensity</th>
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<tbody>
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<tr>
<td>NRM</td>
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<tr>
<td>Haplo-identical</td>
<td>1.00</td>
<td>1.00</td>
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<tr>
<td>MUD</td>
<td>1.07; p=0.82</td>
<td>2.35; p=0.03</td>
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<tr>
<td>Relapse</td>
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<tr>
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<td>1.00</td>
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<tr>
<td>MUD</td>
<td>0.88; p=0.88</td>
<td>0.76; p=0.09</td>
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<tr>
<td>Survival</td>
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<tr>
<td>Haplo-identical</td>
<td>1.00</td>
<td>1.00</td>
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<tr>
<td>MUD</td>
<td>0.93; p=0.61</td>
<td>1.13; p=0.46</td>
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Blood 2015
Leukemia Free Survival
Adjusted for DRI, performance score, secondary AML

Myeloablative

- MUD 42% (40-45)
- HAPLO 41% (32-51)

Reduced Intensity

- MUD 37% (33-40)
- HAPLO 35% (25-45)

HR 0.98 (95% CI 0.75-1.27), p=0.87

HR 0.98 (95% CI 0.74-1.30), p=0.89
Haplo vs UCBT

A prospective randomized trial is currently ongoing in North America comparing unmanipulated Haplo and double UCBT in the RIC setting with TBI Cy Flu as conditioning regimen and PTCy as GvHD prophylaxis for Haploidentical Tx

RESULTS EXPECTED IN 2019
ORIGINAL ARTICLE

Comparison of outcomes after unrelated cord blood and unmanipulated haploidentical stem cell transplantation in adults with acute leukemia

A Ruggeri1,2,3, M Labopin1,4, G Sanz5, S Piemontese6, W Arcese7, A Bacigalupo8, D Blaise9, A Bosi10, H Huang11, D Karakasis12, Y Koc13, M Michallet14, A Picardi7, J Sanz5, S Santarone15, H Sengelov16, J Sierra17, L Vincent18, F Volt3, A Nagler19,20, E Gluckman3,21, F Ciceri6, V Rocha3,22 and M Mohty1,2,4 on behalf of Eurocord, Cord Blood Committee of Cellular Therapy and Immunobiology working party-EBMT, ALWP-EBMT study

Leukemia doi:10.1038/leu.2015.98; accepted article preview online April 17, 2015
Selection criteria

• Adults with acute leukemia
• Transplanted in EBMT centers (2007-2012)
• Single CBT (TNC at freezing $\geq 2.5 \times 10^7$/Kg) or Double CBT or HaploSCT ( $\geq 2$ HLA MM)
• Myeloablative or reduced intensity conditioning regimen
• First alloSCT

518 non TCD Haplo and 928 CBT
Results - UCBT vs Haplo for adults with AL - Neutrophil Engraftment

92 ± 2%

84 ± 2%

Median time to engraftment:
17 days for HaploSCT and 23 days for CBT, p=0.003
UCBT vs Haplo for adults with AML

- cGVHD
  - Haplo (n=360): 29% ± 5
  - CBT (n=558): 24% ± 4
  - p = 0.18

- Relapse
  - Haplo (n=360): 41% ± 5
  - CBT (n=558): 32% ± 4
  - p = 0.008

- NRM
  - Haplo (n=360): 30% ± 5
  - CBT (n=558): 27% ± 5
  - p = 0.09

- LFS
  - Haplo (n=360): 38% ± 4
  - CBT (n=558): 32% ± 5
UCBT vs Haplo for adults with ALL

**cGVHD**
- Haplo (n=158) vs CBT (n=370)
- Cumulative Incidence of chronic GVHD
- p = 0.17
- 31% ± 5 vs 25% ± 4

**Relapse**
- Cumulative Incidence of relapse
- p = 0.02
- 37% ± 5 vs 27% ± 4

**NRM**
- Cumulative Incidence of NRM
- p = 0.22
- 39% ± 5 vs 35% ± 5

**LFS**
- Leukemia Free Survival
- p = 0.49
- 34% ± 4 vs 28% ± 5
Current status of Haplo- Conclusions

- 15.6% of alloSCT in Europe are mismatch related (constantly increasing – 25% increase in 2014 vs. 2013)
- 2456 mismatch related alloSCT were performed in Europe in 2014
- Disease status is one of the main prognostic factor for outcomes
- Need for the development of transplant strategies in advanced phase AL:
  - Sequential approach combined with post-transplant immuno-intervention
- Similar results with the use of BM or PBSC and RIC or MAC
  - Higher relapse risk with RIC
- Number of HLA mismatches does not influence Haplo outcomes
Current status of Haplo- Conclusions II

- DLI administration after Haplo is feasible with no severe toxicities
- Delayed immune reconstitution and infectious complications are reported
- Single centers and registry based studies report comparable results between Haplo, sibling donor and unrelated donors
- Strategies to enhance immunerecovery after Haplo are needed
- Center experience and policy
Acknowledgment

• ALL EBMT centers
• ALWP EBMT office
• Myriam Labopin, Simona Piemontese, Francesca Lorentino, Fabio Ciceri, Mohamad Mohty, Arnon Nagler
• Emanuelle Polge and all ALWP study coordinators