Donor and stem cell source selection

21 November 2013
E. Baudoux
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• Introduction
• HPC sources and donor types
• HLA and matching
• Unrelated donor searches
• Donor choice and eligibility
• Search strategies (Sibling, UD, CB, no Haplo)
Hematopoietic stem cell transplantation (HSCT) has become an accepted therapy for many congenital or acquired disorders of the hematopoietic system and has seen major changes in indications and use of transplant techniques over the years.

**Figure 1:** Increase in the number of unrelated HSCT during the years 1990 and 2009.
Statement by the Worldwide Network for Blood & Marrow Transplantation (WBMT)

Up to end of December 2012: 1 million HSCT have been performed worldwide
Number of stem cell donors and cord blood units worldwide

- Any available donor, if any
- Best available donor or CB
- No alternative to donors

≈ 22M stem cell donors
594,000 CBU’s

Data from BMDW - Bone Marrow Donors Worldwide
Structure
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• Search strategies (Sibling, UD, CB, no Haplo)
Bone marrow
Hematopoietic Stem Cell (HPC) sources

BM

PBSC

CB
Bone marrow collection

<table>
<thead>
<tr>
<th>Anticoagulant type</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenine Citrate Dextrose-A (ACD-A)</td>
<td>10-15mL/100 mL BM</td>
</tr>
<tr>
<td>Heparin</td>
<td>10U/mL BM</td>
</tr>
</tbody>
</table>

Target 3-4 \( \times 10^8 \) NC/kg
Peripheral stem cell collection

- Continuous flow cell separator
- Transportable equipment ➔ bedside collection allowed
- No general anesthesia
- Peripheral or central vein
- Disposable Kits disposables, closed circuit
- Flexible settings
- Quickly metabolised anticoagulant, low systemic effects
- Collection in adults and children 10 ➔ 100+ Kg

<table>
<thead>
<tr>
<th>HPC, Apheresis</th>
<th>Ideal dose</th>
<th>Minimal dose</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autologous</td>
<td>5 x 10^6 CD34/kg</td>
<td>2 x 10^6 CD34/kg</td>
<td>• x 2 if tandem autologous transplant foreseen</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• x 1.5 if processing is foreseen (selection, depletion)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• CFU-GM useful (&gt; 20 x 10^4/kg ?) if available cell dose low or multiple apheresis</td>
</tr>
<tr>
<td>Allogeneic</td>
<td>Highest possible</td>
<td>2 x 10^6 CD34/kg</td>
<td>x 1.5 if processing is foreseen (selection, depletion)</td>
</tr>
<tr>
<td></td>
<td>CD34/kg (&gt; 5 x 10^6 CD34/kg)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Cord blood collection
DONOR TYPES

• Matched Sibling Donor
  – Usually HLA identical brother or sister
    (Sometimes as cord blood donor)

• Matched Unrelated Donor

• Unrelated CB Donor

• (Haploidentical Donor)
## Donor/source of HPC

<table>
<thead>
<tr>
<th>Source</th>
<th>Autologous (Patient)</th>
<th>Allogeneic</th>
</tr>
</thead>
<tbody>
<tr>
<td>BM (HPC, M)</td>
<td>Patient</td>
<td>Sibling ➔ Donor registries</td>
</tr>
<tr>
<td>PBSC (HPC, A)</td>
<td>Patient</td>
<td>Sibling ➔ Donor registries</td>
</tr>
<tr>
<td>Cord Blood (HPC, CB)</td>
<td>Sibling ➔ CB Banks Donor registries</td>
<td></td>
</tr>
</tbody>
</table>
## DONOR

### Adult versus CB unrelated donor

<table>
<thead>
<tr>
<th></th>
<th>Adult volunteer</th>
<th>Cord blood</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Engraftment</strong></td>
<td>Rapid</td>
<td>Slow</td>
</tr>
<tr>
<td><strong>Risk of GVHD</strong></td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td><strong>HLA compatibility</strong></td>
<td>8+ out of 8</td>
<td>4-5 out of 6</td>
</tr>
<tr>
<td><strong>LIMITATION</strong></td>
<td>HLA</td>
<td>CELLULARITY</td>
</tr>
</tbody>
</table>
## DONOR

### Adult versus CB unrelated donor

<table>
<thead>
<tr>
<th></th>
<th>Adult volunteer</th>
<th>Cord blood</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Supply</strong></td>
<td>10% loss/year</td>
<td>unlimited</td>
</tr>
<tr>
<td><strong>Delay</strong></td>
<td>6 months</td>
<td>Immediately available</td>
</tr>
<tr>
<td><strong>Risk to donor</strong></td>
<td>anesthesia (BM)</td>
<td>none</td>
</tr>
<tr>
<td><strong>NC dose</strong></td>
<td>OK</td>
<td>OK for children</td>
</tr>
<tr>
<td><strong>Engraftment</strong></td>
<td>Rapid</td>
<td>Slow</td>
</tr>
<tr>
<td><strong>Risk of GVHD</strong></td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td><strong>HLA compatibility</strong></td>
<td>8+ out of 8</td>
<td>4-5 out of 6</td>
</tr>
<tr>
<td><strong>Probability</strong></td>
<td>65%</td>
<td>100%</td>
</tr>
<tr>
<td><strong>LIMITATION</strong></td>
<td>HLA</td>
<td>CELLULARITY</td>
</tr>
</tbody>
</table>
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• **HLA and matching**
  • Unrelated donor searches
  • Donor choice and eligibility
  • Search strategies (Sibling, UD, CB, no Haplo)
Human Leucocyte Antigen
DONOR
HLA system

• 12 genes on short arm of chromosome 6 :
  – 3 HLA class 1 gene (A, B, C) : monomeric Ag (A, B, C)
  – 9 HLA class 2 genes (DRA1, DRB1, DRB3, DRB4, DRB5, DQA1, DQB1, DPA1, DPB1)
  – DRB3, DRB4, DRB5 genes are mutually exclusive, are present only on certain haplotypes, in relation with particular DR Ag (DR52, DR53, DR51)

• Extreme polymorphism :
  – Antigenic level : A, B, C, DR, DQ antigens
  – Allelic level : A, B, C, DRA1, DRB1, DRB3, DRB4, DRB5, DQA1, DQB1, DPA1, DPB1 genes.
    Number of identified alleles increases constantly
HLA alleles of importance for HSCT
Assigned April 2012

- Range: $10^{23}$ genotypes
- Most frequent haplotype: A 01-B 08-DRB 0301 (6% of caucasians)

<table>
<thead>
<tr>
<th>Locus</th>
<th>N Alleles</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>1884</td>
</tr>
<tr>
<td>B</td>
<td>2490</td>
</tr>
<tr>
<td>C</td>
<td>1384</td>
</tr>
<tr>
<td>DRB1</td>
<td>1194</td>
</tr>
<tr>
<td>DQB1</td>
<td>165</td>
</tr>
</tbody>
</table>
DONOR
HLA incompatibility

• Level of incompatibility:
  – Antigenic (2-digit): A*02 vs A*03
  – Allelic (4-digit): A*02:01 vs A*02:02

• Direction of incompatibility:
  – GVH direction
  – Rejection direction
  – Both directions (most frequent)
DONOR
HLA typing

• Over $10^{23}$ genotypes

• Some alleles and some combinations of HLA alleles (haplotypes) are rare and others frequent

  Most frequent haplotype: A01-B08-DRB0301 (6% of caucasians)

• To make sure 2 siblings are genotypically identical, parental typing is necessary to identify haplotypes

• If one of the parents is homozygous at Ag level, low resolution typing does not allow verification of genotypic identity between donor and recipient
DONOR
HLA compatibility

• Degree of compatibility :
  – 12/12 : A-B-C-DRB1-DQB1-DPB1 (not much used)
  – 10/10 : A-B-C-DRB1-DQB1 (generally by high resolution typing)
  – 8/8 : A-B-DRB1-DQB1 (not much used)
  – 6/6 : A-B-DRB1 (generally by low resolution typing)

• Type of compatibility :
  – Genotypic : donor and recipient have received same 2 haplotypes from their parents (twins, siblings)
  – Phenotypic : donor and recipient have inherited one haplotype but not the other or are unrelated
### Donor

<table>
<thead>
<tr>
<th></th>
<th>A* 02:02</th>
<th>A* 02:02</th>
<th>A* 02:02</th>
<th>A* 04:03</th>
</tr>
</thead>
<tbody>
<tr>
<td>B*</td>
<td>04:01</td>
<td>35:01</td>
<td>44:01</td>
<td>35:01</td>
</tr>
<tr>
<td>C*</td>
<td>03:03</td>
<td>04:03</td>
<td>04:03</td>
<td>04:03</td>
</tr>
<tr>
<td>DRB1*</td>
<td>01:01</td>
<td>08:02</td>
<td>01:02</td>
<td>08:02</td>
</tr>
<tr>
<td>DQB1*</td>
<td>02:03</td>
<td>04:03</td>
<td>02:03</td>
<td>04:03</td>
</tr>
</tbody>
</table>

### Patient

<table>
<thead>
<tr>
<th></th>
<th>A* 02:02</th>
<th>A* 02:02</th>
<th>A* 02:02</th>
<th>A* 04:03</th>
</tr>
</thead>
<tbody>
<tr>
<td>B*</td>
<td>04:01</td>
<td>35:01</td>
<td>44:01</td>
<td>35:01</td>
</tr>
<tr>
<td>C*</td>
<td>03:03</td>
<td>04:03</td>
<td>04:03</td>
<td>04:03</td>
</tr>
<tr>
<td>DRB1*</td>
<td>01:02</td>
<td>08:02</td>
<td>01:02</td>
<td>08:02</td>
</tr>
<tr>
<td>DQB1*</td>
<td>02:03</td>
<td>04:03</td>
<td>02:03</td>
<td>04:03</td>
</tr>
</tbody>
</table>

### Rejection

<table>
<thead>
<tr>
<th>Ag</th>
<th>Allele</th>
<th>Donor</th>
<th>Patient</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>B</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>C</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>DRB1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>DQB1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>0</td>
<td>0.5</td>
<td>1</td>
<td>0.5</td>
</tr>
</tbody>
</table>

### GVHD

<table>
<thead>
<tr>
<th>Ag</th>
<th>Allele</th>
<th>Donor</th>
<th>Patient</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0.5</td>
</tr>
<tr>
<td>B</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>C</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>DRB1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>DQB1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>1</td>
<td>0.5</td>
<td>1</td>
<td>0.5</td>
</tr>
</tbody>
</table>
DONOR

HLA compatibility : genotypic

Mother

| A 2 | B 44 | DR 3 | A 1 | B 15 | DR 11 |

Father

| A 3 | B 27 | DR 15 | A 31 | B 16 | DR 9 |

Sibling 1

| A 2 | B 44 | DR 3 | A 3 | B 27 | DR 15 |

Sibling 2

| A 2 | B 44 | DR 3 | A 31 | B 16 | DR 9 |

Patient

| A 2 | B 44 | DR 3 | A 3 | B 27 | DR 15 |
# DONOR

## Minimal and ideal compatibility

<table>
<thead>
<tr>
<th>DONOR TYPE</th>
<th>MATCH LEVEL</th>
<th>REMARK</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identical twin</td>
<td>By definition genotypically identical</td>
<td></td>
</tr>
<tr>
<td>Brother/sister (sibling) or other family donor</td>
<td>6/6</td>
<td>5/6 IF one haplotype is genotypically identical. If not, see MUD</td>
</tr>
<tr>
<td>Unrelated (MUD)</td>
<td>10/10</td>
<td>8/10 allelic*</td>
</tr>
<tr>
<td>Cord blood</td>
<td>6/6</td>
<td>4/6 antigenic</td>
</tr>
</tbody>
</table>
| Haploidentical                                  | 1 haplotype identical  
Other haplotype: any |                                                                 |

(*) Minimum 8/10 allelic:

- 1 antigenic MM (9/10)
- 1 allelic + 1 antigenic MM (8.5/10)
- 2 allelic MM (9/10)
- 1 antigenic + 1 antigenic DQB1 (8/10)
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DONOR
Search for unrelated donors

• Simultaneous VUD and CB search: based on type of HSCT (mini vs conventional) and donor selection criteria.
• BMDW (Bone Marrow Donor Worldwide): all UD/CB listed by HLA compatibility with patient.
• MDP-B (Marrow Donor Program-Belgium): Prometheus IT system and EMDIS network connecting with foreign registries including NMDP-USA.
• Netcord: CBB network, global search with NMDP-USA. Belgian hub is MDP-B.
• Confirmatory HLA typing (CT) in Liège on each donor before start of conditionning.
MDPB-REGISTRY

- MDP-B Registry (Prometheus)
  - Unrelated donors
  - Belgian Patients
- 7 donor centers >63 000 Donors
- 5 Cord blood banks >17 000 CBUs
- 9 Transplant centers (national patients)
- Searching for national donors
- Searching for International donors

- Internet
- EMDIS

- 71 INTERNATIONAL REGISTRIES
- 48 CB BANKS
- >22 M DONORS
- >590 000 CBUS

5 Cord blood banks >17 000 CBUs
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• **Donor choice and eligibility**
• Search strategies (Sibling, UD, CB, no Haplo)
Choice: donor selection among a potential donors, based on:
- HLA
- Age, sex, CMV, ABO ...
- Donor preferences

Eligibility: donor acceptance, based on absence of contra-indication (non-conformity):
- Donor safety
- Patient safety
DONOR

Donor eligibility : non-conformity

• Donor non conformity with any eligibility criteria may constitute:
  – Absolute contraindication to cell donation: dans ce cas, le besoin médical urgent (UMN, Urgent Medical Need) n’est pas possible.
  – Contre-indication relative au don de cellules : dans ce cas, le besoin médical urgent (UMN, Urgent Medical Need) est possible, moyennant décision du comité de greffe après éventuels avis spécialisés.
  – Précaution : le don de cellules est acceptable, mais des mesures complémentaires peuvent devoir être prises pendant le déroulement de la collecte et/ou de la greffe.
## Eligibility criteria

<table>
<thead>
<tr>
<th>Criteria (examples)</th>
<th>Regarding donor safety</th>
<th>Regarding recipient safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Autoimmune disease</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Anticoagulant therapy</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Coronarian disease</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>History of Cancer</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Genetic disease</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Vaccines</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>History of infection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parasitic</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Microbial</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Viral</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>CJD/BSE risk evaluation</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Blood and marrow disorders</td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>
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Strategy of alternative stem cell donor

- HLA identical sibling or HLA matched BM or PBSC donor (10/10) → Transplantation
  - NO
  - Simultaneous search for
    - Unrelated Cord Blood
    - Haploidentical familiar donor
  - Mismatched unrelated donor (9/10 HLA matched)
    - Few data available. Lack of study comparing outcomes of UCBT or Haplo with 9/10 MUD

If urgency in transplant (<3 months from last remission) go to transplant with UCB or Haplo

UCBT

- Use of Single or Double units according to TNC at collection and number of HLA mismatches*
- Use of myeloablative or reduced intensity conditioning regimen according to age and patients comorbidity

Haplo

- Use of CD34+ selected megadose*
- Choice mother, when available as donor
- Selection of KIR mismatched donor
- Use of myeloablative regimen
- Lack of possibility to perform reduced intensity conditioning regimen

*Cell dose according to HLA mismatches
  - HLA: 0-1/6
  - HLA: 2/6
  - >3x10^7/kg TNC
  - >4x10^7/kg TNC
  - >1x10^8/kg CD34
  - >2x10^8/kg CD34

* T cell depleted graft: >10x10^6/kg CD34, 1x10^6/kg CD34
Finding a MUD
Search success rates and duration

- Search success rates
  (>20 million VUDs)
  - 8/8 match: 40 – 60%
  - 1 antigen mismatch: 60 – 90%
- Median search duration: 22 d – 2.5 mo
- Median time to transplant: 2 – 4 mo
Actuarial probability of finding a 7/8 or 8/8 MUD in Spain (Memoria REDMO 2009)

- 3 m → 44%
- 6 m → 57%
- 12 m → 65%
- 70% is the probability of finding an alternative donor necessary.
## Alternative donor allogeneic transplantation: criteria for choosing MUD vs. CBT vs. Haplo

<table>
<thead>
<tr>
<th></th>
<th>UBMT</th>
<th>UCBT</th>
<th>Haplo-HSCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Information on A+B+DRB1 (DNA) typing (%)</td>
<td>16-56</td>
<td>~80</td>
<td>100</td>
</tr>
<tr>
<td>Median search time (months)</td>
<td>3-6</td>
<td>&lt;1</td>
<td>Nil</td>
</tr>
<tr>
<td>Donors identified but not available (%)</td>
<td>20-30</td>
<td>~1</td>
<td>None</td>
</tr>
<tr>
<td>Rare haplotypes represented (%)</td>
<td>2-10</td>
<td>20</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Main limiting factor to graft acquisition</td>
<td>HLA identity</td>
<td>Cell dose</td>
<td>Poor mobilization</td>
</tr>
<tr>
<td>Ease of rearranging the date of cell infusion</td>
<td>Difficult</td>
<td>Easy</td>
<td>Easy</td>
</tr>
<tr>
<td>Potential for immunotherapy</td>
<td>Yes</td>
<td>No</td>
<td>Yes (limited)</td>
</tr>
<tr>
<td>Potential for viral transmission to recipient</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Potential for congenital disease transmission to recipient</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Risk for the donor</td>
<td>Very low</td>
<td>No</td>
<td>Very low</td>
</tr>
<tr>
<td>Main problems to be overcome</td>
<td>GvHD</td>
<td>Graft failure, delayed immune recovery</td>
<td>Delayed immune recovery, lack of T-cell-mediated GVL effect</td>
</tr>
</tbody>
</table>

Abbreviations: Haplo-HSCT=haploidentical hematopoietic stem cell transplantation; UBMT=unrelated donor BM transplantation; UCBT=umbilical cord blood transplantation.

* Modified from Grewal et al. 4
Look at the number of cells in MAC, RIC:
✓ $>2.5 \times 10^7$ NC/kg and or $>1 \times 10^5$ CD34+/kg

Look at HLA matches:
✓ 0-1 mm better than 2 avoid 3-4 mm
✓ Prefer class I mismatches than class II
✓ Include HLA C typing, avoiding C mismatches
✓ Allele typing of HLA -A and –B (++) in case of 4/6 CBU

Then adapt to graft indication:
✓ If the minimum number of cells for a single UCBT is not achieved, a double UCBT should be considered
✓ Malignant diseases: cell dose is the best prognostic factor because HLA differences reduce relapse (GVL)
✓ Non malignant diseases: increase cell dose ($>4.0 \times 10^7$ NC/kg ) and find the best HLA match

Other considerations, if several CBU are available consider:
✓ Cord Blood Bank accreditation status and location
✓ ABO compatibility
✓ NIMA and KIR status
Schema of how we select CB units.

Evaluate search reports for units 4-6/6 HLA-matched with TNC ≥ 2.0 x 10^7/kg.

Review information & bank of origin for each unit.
Obtain missing unit information.
Request CT of units of interest.
Prepare CB Search Summary Report (Figure 1).

-review CTs: update Search Summary.

Rank units according to HLA-A,-B antigen, -DRB1 allele match (Figure 1). List highest to lowest TNC within each match grade (correct for RBC if needed).

1st choice

6/6 units:
Choose largest TNC.

2nd choice

5/6 units:
Choose largest TNC.

3rd choice

4/6 units:
Choose largest TNC.

Make final selection of unit(s) of graft (units 1a & 1b if double unit graft).

Prepare domestic back-up unit(s).

Plan shipment(s).

References

• Barker J et al
  How I treat: the selection and acquisition of unrelated cord blood grafts
  Blood 2011 117: 2332-2339

• Eapen M et al
  Effect of Graft Source on Unrelated Donor Haemopoietic Stem-Cell Transplantation in
  Adults with Acute Leukemia: A Retrospective Analysis
  Lancet Oncol. 2010 July ; 11(7): 653–660

• Stevens C et al.
  HLA mismatch direction in cord blood transplantation: impact on outcome and
  implications for cord blood unit selection
  Blood 2011 118: 3969-3978

• Ponce DM et al
  The Use of Back-up Units to Enhance the Safety of Unrelated Donor Cord Blood
  Transplantation

• ESH
  HSC transplantation
  The EBMT Handbook, 6th Edition 2012 Chapters 6-7
Aknowledgements

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