Graft source and donor Algorithm

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Scientific Director of Eurocord
Estimate number of patients with an indication of an allogeneic hematopoietic stem cell transplants

- HLA identical sibling donor: 30%
- Related 1 HLA incompatible: 40%
- Unrelated BM or PB donor: 27%
- No donor: 3%

Haplo Cord Blood
Conditional probability of finding an 10 of 10 allele level matched unrelated adult donor in the Swiss registry for a Caucasian was found in 69% of the patients (high probability), but in only 11% of the patients with a low-probability estimate ($P<0.00001$) (Tiercy JM et al, BMT 2007)

Conditional probability of finding an 8 of 8 allele level matched unrelated adult donor is

- 51% for Caucasians
- 30% for Hispanics (certainly lower in LA)
- 20% for Asians
- 17% for African Americans

(NMDP data)
### Searching and identifying an alternative stem cell donor

#### Main criteria to be considered

<table>
<thead>
<tr>
<th>Category</th>
<th>UBMT</th>
<th>UCBT</th>
<th>Haplo-HSCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Information on A + B + DRB1 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>immediate</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 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</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Risk for the donor</td>
<td>Low</td>
<td>No</td>
<td>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>

Age and Disease Adapted Donor Choice

Children or Adults?

Non-malignant or Malignant disorders?
Age and Disease adapted donor choice

Children
Non malignant disorders
Children with Hurler disease
Disease Free Survival by type of donor and HLA

HLA identical sibling 81±6% or HLA 6/6 unrelated CB 81±8%

HLA matched unrelated donor 10/10 66±7% or CB 5/6 68±6%

Unrelated CB 4/6 57±9% (if high CD34 cell dose EFS=73±13%)

HLA matched low resolution or mismatched (antigen or allelic level) (incl. T cell depleted) 41±7%

P=0.004

Boelens J and Rocha V on behalf of Eurocord, CIBMTR, Minneapolis and Duke University
Overall Survival after Unrelated Cord Blood or HLA Mismatched Family donor for patients with SCID

\[ P (\text{Cox}): 0.61 \]

Fernandes et al., Blood 2012
Overall Survival after Unrelated Transplants for aplastic anemia and Other Inherited Bone Marrow Failure Disease, Age ≤16, 1996-2006 - by Graft Type -

- Bone marrow (N = 410, 62% @ 2-years)
- Cord blood (N = 222, 45% @ 2-years)

P = 0.0001 @ 2-years
Strategy of alternative stem cell donor in children with non-malignant disorders

Metabolic Disorders (better results in early ages)
HLA identical = Unrelated 6/6 CB > MUD 10/10 = UCB 5/6 > CB 4/6 high cell dose

Primary Immunodeficiencies (Urgent situations)
HLA identical > UCB = HLA mismatched Donor = MUD (10/10) (rare)

Aplastic Anemia (congenital or acquired)
HLA identical > MUD 10/10 > MUD 9/10 >> CB (6/6 or 5/6 cell dose > 4.5x10^7/Kg)
Haplo HSCT under investigation

Hemoglobinopathies
HLA identical, other alternative donors under investigation

In cases of unrelated donors always ask for BM cells
Do not forget to search for antibodies against HLA in cases of HLA mismatched HSCT
Age and Disease adapted donor choice

Children
Malignant disorders
Unrelated Cord Blood versus allele typing
Unrelated Bone Marrow Transplants in Children with Acute Leukemia

M Eapen et al, Lancet 2007
Neutrophil Recovery

- BM (n=116), 97%
- CB matched (n=35), 85%
- CB MM high dose >3x10^7/kg (n=362), 79%
- CB MM low dose <3.0x10^7/kg (n=97), 64%
Leukemia-free Survival

Adjusted Probability, %

Months

CB matched (n=35) 60%
CB 1-Ag MM >3.0x10^7/kg (n=157) 45%
BM matched (n=116) 38%
CB 2-Ag MM (n=267) 33%
CB 1-Ag MM >3.0x10^7/kg (n=44) 35%

Strategy of alternative stem cell donor in children with malignant disorders

- High resolution HLA typing
  - To be considered Haplo T-depleted in experienced centres. Cy after??
- Simultaneous search
- Cord Blood Banks
  - NC dose collected to be increased with number of mismatches (single or double)
    - >2.5x10^7/kg NC
    - >1x10^5/kg CD34
    - HLA: 0-1/6
  - >3.5x10^7/kg NC
  - >2x10^5/kg CD34
  - HLA: 2/6
- Bone Marrow donor registries
  - <8/8 or >3 mths delay for AL)
  - Bone Marrow donor registries
  - HLA 8/8 or 9/10 or 10/10
- UCBT
Age, Disease and disease status adapted donor choice

Adults
Malignant disorders:
Acute Leukemias (AML, ALL)
MDS
Lymphoid malignancies

In remission or not

(Myeloablative or reduced intensity)

Cord Blood vs Unrelated Bone Marrow

6/6

ENGRAFTMENT

ACUTE GVHD

CHRONIC GVHD

EARLY TRM

RELAPSE

SURVIVAL
316 adults undergoing UCBT (mostly 1 or 2 antigen-mismatched), and 996 adults undergoing UBMT (almost entirely fully matched with the recipient), were analyzed. T-cell-depleted UBMT was excluded; where data were available, only fully matched UBMT was used in the analysis.

RESULTS

For adults, transplantation-related mortality (pooled estimate, 1.04; 95% CI = 0.52-2.08; P = .91) and disease-free survival (DFS) (pooled estimate, 0.59; 95% CI = 0.18-1.96; P = .39) were not statistically different.

Effect of Stem Cell Source on Transplant Outcomes in Adults with Acute Leukemia

A Comparison of Unrelated Bone Marrow, Peripheral Blood Progenitor Cells and Single Cord Blood

From the Center for International Blood and Marrow Transplant Research, Eurocord-ALWP-EBMT and New York Blood Center

M Eapen, V Rocha Lancet Oncology 2010
Leukemia-free Survival
-Adjusted for Disease Status at Transplantation-

Matched BM vs. CB  RR 0.87, p=0.254
Matched PBPC vs. CB RR 0.89, p=0.177

BM matched, 41%
PBPC matched, 39%
CB, 33%

PBPC mismatched, 34%
BM mismatched, 34%

Not in remission at HCT, RR 2.40, p<0.001
Haplo Transplants

To be considered....

IMPACT OF KIR MATCHING (IN AML PATIENTS), CD34 CELL DOSE, MOTHER AS A DONOR AND CENTRE EXPERIENCE

New developments of Haplo-HSCT
GSCF Primed BM transplants, T cell replete with increased immunosuppression in vivo (Chinese approach and post CY) Immunotherapy
Possible algorithm of donor choice in adults with high risk AL with an indication for allogeneic transplantation (Ruggeri A and Rocha V, 2010)

| HLA identical sibling or HLA matched BM or PBSC donor (10/10) | Mismatched unrelated donor (9/10 HLA matched) |
| Simultaneous search for Unrelated Cord Blood | Few data available. Lack of study comparing outcomes of UCBT or Haplo with 9/10 MUD |
| Haploidentical familiar donor | |
| If urgency in transplant (<3 months from last remission) go to transplant with UCB or Haplo |

- 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

*Cell dose according to HLA mismatches
HLA: 0-1/6 HLA: 2/6
>3x10^7/kg TNC > 4x10^7/kg TNC
>1x10^5/kg CD34 >2x10^5/kg CD34

* T cell depleted graft: >10x10^6/kg CD34, 1x10^6/kg CD3
HLA diversity in LA
Tracking human migrations by the analysis of the distribution of HLA alleles, lineages and haplotypes in closed and open populations

Marcelo A. Fernandez Vina, Jill A. Hollenbach, Kirsten E. Lyke, Marcelo B. Sztein, Martin Maers, William Kiltz, Pedro Cano, Steven Mack, Richard Single, Chaim Brautbar, Shosahna Israel, Eduardo Raimondi, Evelyne Khohaty, Adlette Inati, Marco Andreani, Manuela Testi, Maria Elisa Moraes, Glenys Thomson, Peter Stastny and Kai Cao

Is the algorithm of graft source and donor the same in different LA countries?

- **Brazil**
  HLA identical siblings > HLA 10/10 or 9/10 > Cord Blood > Haplo

- **Chile**
  HLA identical siblings > CBU > Haplo

- **Mexico**
  HLA identical siblings > HLA 10/10 or 9/10 > Cord Blood > Haplo
<table>
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<tr>
<th>Registry</th>
<th>Registry Code</th>
<th>Total</th>
<th>ABDR</th>
<th>%ABDR Typed</th>
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</table>
Discussion on alternative donors in LA

Centers with expertise in Unrelated, CB and Haplo HSCT

- Establishment of Donor Registries/ costs
- (Brazil, Argentina, Mexico, CBB Chile and Uruguay)
- Cord blood banks/ costs and costs of CBU and transplants (delay engraftment and viral infections)
- Haplo transplants
  + and - selection (expertise and costs, problems, relapse, viral infections)

CY after: still short follow up (interesting approach)