Umbilical Cord blood transplantation

- Background
  - History
  - Clinical results in children and adults
  - Importance of cell dose and HLA

- Umbilical cord blood forms
  - Cord blood bank information
  - Transplant center information
First cord blood transplant

Past and Present of Cord Blood Transplants

1989  First Cord blood transplant
1989-92  Clinical observation that GVHD was reduced in HLA incompatible CBT
1993-95  Feasibility of HLA incompatible unrelated cord blood transplants
1995  Establishment of Eurocord group
1997  Nucleated cell dose more important factor for engraftment and survival, influence of HLA on engraftment
1998  Large series of UCBT = confirmation of cell dose and HLA
>2000  Retrospective comparisons between UBMT and UCBT
2002  Use of cord blood cells in adults with promising results
2003  Criteria of cord blood choice and indications
2004  Use of double cord and RIC regimen in adults
2004-05  Isolation of USSC from umbilical cord blood
2004-05  Comparable results between unrelated CBT and UBMT in adults
2006  More adults than children transplanted with cord blood cells
2007  Allele matched UBMT compared to UCBT in children with AL
Estimate number of patients with an indication of an allogeneic hematopoietic stem cell transplants

![Pie chart showing distribution of patients by type of donor]

- **27%** HLA identical sibling donor
- **30%** Related 1 HLA incompatible
- **3%** Unrelated BM or PB donor (9 or 10 out of 10)
- **40%** no donor

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DEVELOPMENT OF STRATEGIES OF STEM CELL TRANSPLANT IN THE ABSENCE OF HLA IDENTICAL SIBLING DONOR

Unrelated HLA matched hematopoietic stem cell donor

- ~ 44,000 donor search process
- 40% of patients relapsed or died before transplant
- ~ 4,000 transplants

(NMDP data)
Searching and identifying an unrelated stem cell donor

<table>
<thead>
<tr>
<th>BM</th>
<th>CB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Information of A+B (serology) +DRB1(DNA) typed</td>
<td>16-56%</td>
</tr>
<tr>
<td>Median search time</td>
<td>3-6 mon</td>
</tr>
<tr>
<td>Donors identified but not available</td>
<td>30%</td>
</tr>
<tr>
<td>Rare Haplotypes represented</td>
<td>2-10%</td>
</tr>
<tr>
<td>Major limiting factors to graft acquisition</td>
<td>HLA match</td>
</tr>
<tr>
<td>Ease of rearranging date of cell infusion</td>
<td>Difficult</td>
</tr>
<tr>
<td>Potential for second HSC graft or DLI from the same donor</td>
<td>Yes</td>
</tr>
<tr>
<td>Potential for viral transmission to recipient congenital diseases</td>
<td>Yes</td>
</tr>
<tr>
<td>Risk to donor</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Advantages and disadvantages

Grewal S et al, modified Blood 2003

~300,000 cord blood units reported to Bone Marrow Donor Worldwide in~ 45 CB banks 2006

<table>
<thead>
<tr>
<th>No. of units</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
</tr>
</tbody>
</table>

USA-Paramus
USA-Michigan
USA-ARCCBP
USA-ARCCBP
USA-Denver
UK-BBMR
Switzerland
Netherlands
Leuven
Israel
Germany
France
Finlande
Dusseldorf
Czekia
Belgium
Austria
Australia
Argentina

Asia Cord (China, Korea, Taiwan, Japan)= 80,000
Unrelated Donor Stem Cell Sources by Recipient Age 1999-2006

Number of CBT / year reported to Eurocord

February 2007

*Still collecting data
Single Unrelated CBT according to the recipient age/year reported to Eurocord

- Children (1176)
- Adults (590)

*Still collecting data

February 2007

Double Unrelated CBT / year reported to Eurocord

- Double CBT n=248

*Still collecting data

February
UNRELATED CORD BLOOD TRANSPLANT
IN CHILDREN

Eurocord Registry

Single UCBT in children with malignancies
N=847

Transplant related mortality according to the period of CBT

1994-1999: 32%+/-3
2000-2002: 24%+/-2
2003-2006: 17%+/-2

p=0.04
### Comparative studies between UCBT and UBMT in children

<table>
<thead>
<tr>
<th></th>
<th>Cord blood</th>
<th>vs</th>
<th>Bone Marrow</th>
</tr>
</thead>
<tbody>
<tr>
<td>ENGRAFTMENT</td>
<td>↓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACUTE GVHD</td>
<td>↓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHRONIC GVHD</td>
<td>↓ ↔</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EARLY TRM</td>
<td>↔ ↑</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RELAPSE</td>
<td>↔</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SURVIVAL</td>
<td>↔ ↑</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### UNRELATED CORD BLOOD TRANSPLANT IN ADULTS

**Results**

Eurocord Registry
Single UCBT in adults with malignancies
N=557

Transplant related mortality according to the period of CBT
1994-1999: 51%+/-5
2000-2002: 34%+/-3
2003-2006: 27%+/-3
p=0.002

Comparative studies between UCBT and UBMT in adults

Cord blood vs Bone Marrow

ENGRAFTMENT
ACUTE GVHD
CHRONIC GVHD
EARLY TRM
RELAPSE
SURVIVAL
Impact of number and type of HLA incompatibilities and cell dose on outcomes of unrelated cord blood transplants for patients with malignant and non-malignant disorders

An Eurocord registry analysis

UCBT malignant disorders (n=929)

TRM according to number of HLA and cell dose

0-1 HLA and cell dose >= 2
2 HLA diff and cell dose >= 2
3-4 HLA diff and cell dose >= 2
0-1 HLA and cell dose < 2
2 HLA diff and cell dose < 2
3-4 HLA diff and cell dose < 2

P< 0.0001
Criteria of donor choice
Recommendations 2007

1. First look at the number of cells:
   $>2.5 \times 10^7$ CN/ kg et/ ou $>1.5 \times 10^5$ CD34+/ kg.

2. Second look at HLA matches
   - 0-1 mm better than 2 avoid 3.4 mm
   - Prefer class I mismatches than class II
   - If no choice increase the number of cells

3. Then adapt to graft indication
   - Malignant diseases: cell dose is the best prognostic factor because HLA differences reduce relapse (GVL)
   - Non malignant diseases: increase cell dose and find the best HLA match.
### Product Transport and Receipt

20. Was this product collected off-site and shipped to your facility?

1. yes  
2. no

<table>
<thead>
<tr>
<th>21. Date of receipt of product at your facility:</th>
<th>Month</th>
<th>Day</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>20</td>
</tr>
</tbody>
</table>

22. Time of receipt of product (24-hour clock):

   Hour: | Minute |
   ---- |--------|
   [     |        |

   1. standard time  
   2. daylight savings time

23. Specify the shipping environment of the product(s):

   1. Frozen gel pack  
   2. Frozen cord blood unit(s)  
   3. Room temperature per transplant center request  
   4. Other

   Temperature:  

   24. Specify shipping environment:

25. (Cord blood product only) Were the secondary containers (e.g., insulated shipping container and unit cassette) intact when they arrived at your center?

1. yes  
2. no
Storage

Shipping Container

- LN2 dry shipper

- Temperature monitoring devices
  - Data loggers
  - Thermal indicators
26. (Cord blood product only) Was the cord blood unit completely frozen when it arrived at your center?
   1. yes
   2. no

27. (Cord blood product only) Was the cord blood unit stored at your center prior to thawing?
   1. yes
   2. no

28. Specify the storage method used for the cord blood unit:
   1. liquid nitrogen
   2. vapor phase
   3. electric freezer

29. Temperature during storage: ______ °C

30. Date storage started:
    Month  Day  Year

31. Was a fresh product received, then cryopreserved at your facility prior to infusion?
   1. yes
   2. no
   3. not applicable, cord blood unit

32. Was the product thawed from a cryopreserved state prior to infusion?
   1. yes
   2. no

33. Was the entire product thawed?
   1. yes
   2. no

34. Was a component of the bag thawed?
   1. yes
   2. no

35. Were there multiple product bags?
   1. yes
   2. no

36. Specify number of bags thawed: ______

37. Date thawing process initiated:
    Month  Day  Year

38. Time at initiation of thaw (24-hour clock):
    Hour  Minute
    1. standard time
    2. daylight savings time

39. Time at completion of thaw (24-hour clock):
    Hour  Minute
    1. standard time
    2. daylight savings time

40. Was the primary container (e.g., cord blood unit bag) intact upon thawing?
   1. yes
   2. no
41. What method was used to thaw the product?
1. no wash — thawed at bedside, then infused
2. OMSO dilution — thawed in lab (added dextran and albumin), then infused
3. washed — thawed in lab (added dextran and albumin), spun and reconstituted in dextran albumin, then infused
4. other method
42. Specify other thaw method:
43. Did any adverse events or incidents occur while thawing the product?
1. yes
2. no

44. Was the product manipulated prior to infusion?
1. yes
2. no

45. Specify portion manipulated:
1. entire product
2. portion of product

46. ABC incompatibility (RBC depletion)
1. yes
2. no

47. Buffy coat preparation (i.e., COBE Spectra)
48. Cell separator (i.e., Ficoll)
49. Density gradient separation (i.e., Ficoll)
50. Plasma removal
51. Sedimentation (i.e., heliprism)
52. Other
53. Specify method:

54. Ex-vivo expansion
1. yes
2. no

55. Genetic manipulation (gene transfer / transduction)
1. yes
2. no

56. Volume reduction
1. yes
2. no

57. CD34+ selection
1. yes
2. no

58. Specify cell selection system used:
1. ClinMACS / ClinMax
2. Isoclad
3. other
59. Specify system:

---

Product Analysis (All Products)

Report product analysis results under each timepoint that testing was performed. If more than two analyses were performed, copy and complete pages 7-8 for each additional analysis.

Product Analysis at 1st Timepoint

Specify the timepoint in the product preparation phase that the product was analyzed:
1. product arrival
2. post-processing, pre-cryopreservation / manipulation
3. post-thaw
4. post-manipulation
5. at infusion (final quantity infused)

Date of product analysis: 142.
Month Day Year

Total volume of product: 143.

Product Analysis at 2nd Timepoint

Specify the timepoint in the product preparation phase that the product was analyzed:
1. product arrival
2. post-processing, pre-cryopreservation / manipulation
3. post-thaw
4. post-manipulation
5. at infusion (final quantity infused)

Date of product analysis: 163.
Month Day Year

Total volume of product: 164.
# Thawing

<table>
<thead>
<tr>
<th>Product Analysis at 1st Timepoint</th>
<th>Product Analysis at 2nd Timepoint</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total Number</strong></td>
<td><strong>Exponent</strong></td>
</tr>
<tr>
<td>Nucleated cells: 144</td>
<td>x 103</td>
</tr>
<tr>
<td>Nonnucleated cells: 145</td>
<td>x 103</td>
</tr>
<tr>
<td>Nucleated red blood cells: 146</td>
<td>x 103</td>
</tr>
<tr>
<td>CD34+ cells: 147</td>
<td>x 103</td>
</tr>
<tr>
<td>CD3+ cells: 148</td>
<td>x 103</td>
</tr>
<tr>
<td>CD4+ cells: 149</td>
<td>x 103</td>
</tr>
<tr>
<td>CD8+ cells: 150</td>
<td>x 103</td>
</tr>
<tr>
<td>Viability of cells: 151</td>
<td>% not tested</td>
</tr>
<tr>
<td>Method of testing cell viability:</td>
<td></td>
</tr>
<tr>
<td>Specify other method:</td>
<td></td>
</tr>
<tr>
<td>Were the colony-forming units (CFU) assessed after thawing? (cold shock product only)</td>
<td>yes</td>
</tr>
<tr>
<td>Were cultures performed before inoculating to test the (Hand-in-hand) for bacterial or fungal infection? (complete for all cell products)</td>
<td>yes</td>
</tr>
<tr>
<td>Specify results:</td>
<td></td>
</tr>
<tr>
<td>If code 198, 290, 219, or 259, specify organism:</td>
<td></td>
</tr>
</tbody>
</table>

---

![Image of thawing procedure](image-url)
Final Product

QC Testing

- QC Samples
  - Nucleated Cell
  - Hematocrit
  - Viability
  - ABO/Rh
  - CFU
  - CD34
  - Sterility
Product Infusion

183. Was more than one product infused? (e.g., marrow and PBSC, PBSC and cord blood, two different cords, etc.)
1. Yes
2. No

184. Was the product infusion described on this insert intended to produce hematopoietic engraftment?
1. Yes
2. No

185. Date of this product infusion:

186. Time product infusion initiated (24-hour clock):

187. Time product infusion completed (24-hour clock):

188. Total volume of product plus additives infused:

189. Specify the route of product infusion:
1. Intravenous
2. Intranasal
3. Intraspinal
4. Other route of infusion

190. Specify route of infusion:

191. Did the volume of infused product include any added agents?
1. Yes
2. No

Specify agent(s) added:
192. Yes
2. No

193. Albumin
194. Antibiotic
195. Deferoxamine
196. Heparin
197. Other

198. Specify agent:

199. Was the entire volume of product infused?
1. Yes
2. No

Specify what happened to the reserved portion:
1. Discarded
2. Cryopreserved for future use
3. Other fate

200. Specify:

201. Specify:

The following questions refer to all stem cell products except for autologous marrow or autologous PBSC products. If this HSCT used an autologous marrow or autologous PBSC product, continue with question 298.

202. Were there any adverse events or incidents associated with the stem cell infusion?
1. Yes
2. No

Specify the following adverse event(s):

- Brachycardia
- Chest tightness / pain
- Chills at time of infusion
- Fever ≤ 103°F within 24 hours of infusion
- Fever > 103°F within 24 hours of infusion
- Gross hemoglobinuria
- Headache
- Hives
- Hypertension
- Hypothesia requiring oxygen (O2) support
- Nausea
- Rigors, mild
- Rigors, severe

Specify Medical Intervention:

Required Medical Intervention?

Resolved?

203. Yes
2. No
204. Yes
2. No
205. Yes
2. No
206. Yes
2. No
207. Yes
2. No
208. Yes
2. No
209. Yes
2. No
210. Yes
2. No
211. Yes
2. No
212. Yes
2. No
213. Yes
2. No
214. Yes
2. No
215. Yes
2. No
216. Yes
2. No
217. Yes
2. No
218. Yes
2. No
219. Yes
2. No
220. Yes
2. No
221. Yes
2. No
222. Yes
2. No
223. Yes
2. No
224. Yes
2. No
225. Yes
2. No
226. Yes
2. No
227. Yes
2. No
228. Yes
2. No
229. Yes
2. No
230. Yes
2. No
231. Yes
2. No
232. Yes
2. No
233. Yes
2. No
234. Yes
2. No
235. Yes
2. No
236. Yes
2. No
237. Yes
2. No
238. Yes
2. No
239. Yes
2. No
240. Yes
2. No
241. Yes
2. No
242. Yes
2. No
243. Yes
2. No
244. Yes
2. No
### Adverse Event and Required Medical Intervention

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Required Medical Intervention?</th>
<th>Resolved?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shortness of breath (SOB)</td>
<td>246. 1 yes 2 no</td>
<td>247. 1 yes 2 no</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>249. 1 yes 2 no</td>
<td>250. 1 yes 2 no</td>
</tr>
<tr>
<td>Vomiting</td>
<td>251. 1 yes 2 no</td>
<td>253. 1 yes 2 no</td>
</tr>
<tr>
<td>Other expected AE</td>
<td>254. 1 yes 2 no</td>
<td>255. Specify:</td>
</tr>
<tr>
<td>Other unexpected AE</td>
<td>258. 1 yes 2 no</td>
<td>259. Specify:</td>
</tr>
</tbody>
</table>

260. In the Medical Director's judgement, was the adverse event a direct result of the infusion?

1  yes  
2  no  

263. Specify the most likely cause of the adverse event:

1  regimen related  
2  product reaction  
3  drug reaction  
4  other illness  
5  other reason  

264. Specify illness: 

265. Specify reason: 

### Donor Demographic Information

**This Donor Demographic Information section (questions 266–287) is to be completed for all stem cell donors except NMDP donors, NMDP cord blood units, and autologous marrow or PBSC donors. If the stem cell product was from an NMDP donor or an autologous marrow or PBSC donor, continue with question 298.**

266. Donor’s date of birth: [ ] [ ] [ ]  [ ] date unknown

267. (Cord blood unit only) Age of mother (approximate): [ ] years  [ ] age unknown

268. (Cord blood unit only) Non-NMDP cord blood unit identification number (CBU ID): 

269. (Cord blood unit only) Is the CBU ID number also the ICCBBA ISBT 128 number?

1  yes  
2  no  

270. (Cord blood unit only) Name of cord blood bank providing CBU: 

271. Donor’s gender:

1  male  
2  female  

272. Was the donor ever pregnant?

1  yes  
2  no  
3  unknown  
4  not applicable, cord blood unit  

273. Specify number of pregnancies: [ ]  [ ] unknown
274. Donor's blood type and Rh factor:
1. A positive
2. A negative
3. B positive
4. B negative
5. AB positive
6. AB negative
7. O positive
8. O negative
9. Unknown

275. Did this donor have a central line placed?
1. Yes
2. No
3. Not applicable, cord blood unit or marrow product
4. Other site

276. Specify the site of the central line placement:
1. Intravenous
2. Subclavian
3. Internal jugular
4. Other site

277. Specify site:

278. Donor's ethnicity:
1. Hispanic or Latino
2. Not Hispanic or Latino
3. Unknown

279. Donor's race: (Mark the group(s) in which the donor is a member. Check all that apply.)

<table>
<thead>
<tr>
<th>White</th>
<th>Black or African American</th>
<th>American Indian or Alaska Native</th>
<th>Native Hawaiian or Other Pacific Islander</th>
</tr>
</thead>
<tbody>
<tr>
<td>7. Western European</td>
<td></td>
<td>22. Korean</td>
<td></td>
</tr>
<tr>
<td>8. White Caribbean</td>
<td></td>
<td>23. Chinese</td>
<td></td>
</tr>
<tr>
<td>9. White South or Central American</td>
<td></td>
<td>24. Vietnamese</td>
<td></td>
</tr>
<tr>
<td>10. Other White</td>
<td></td>
<td>25. Other Southeast Asian</td>
<td></td>
</tr>
</tbody>
</table>

280. What is the relationship of the donor to the recipient?
1. Sibling
2. Recipient's child
3. Other relative
4. Unrelated

281. Specify the relationship of the donor to the recipient:
1. Parent
2. Sibling
3. Cousin
4. Other relative

282. Specify relationship:

283. Was the donor / product tested for potentially transplantable genetic diseases?
1. Yes
2. No
3. Unknown

Specify disease(s) tested:
284. Yes 2 No Sickle cell anemia
285. Yes 2 No Thalassemia
286. Yes 2 No Other

287. Specify genetic disease: ____________________________