Cord Blood Transplant

E. Gluckman
Eurocord
ESH-EBMT training course
Vienna 2014
Background

• Since 1988, umbilical cord blood (CB) has been successfully used to treat children and adults needing stem cell transplantation

• CB is easily collected (non-invasive), provides a rapidly available source of stem cells

• No risk for the donor and few ethical problems

• CB stem cells are immature cells that allow for a higher number of HLA mismatches than other standard cell sources

• Clinical outcomes after CB HSCT are similar to outcomes to HSCT using bone marrow or PBSC
Background

• In the past, CB was routinely discarded with the placenta as medical waste after a baby’s birth and it was considered property of the hospital.

• Once the therapeutics characteristics of the CB were identified, informed consent for the collection and storage of CB became necessary.
Cord Blood Transplantation Advantages

• More than 25 years experience
• Immediate availability, absence of donor risk, HLA mismatches accepted
• General applicability for children and adults with malignant and non-malignant disorders
• Genetically diverse populations are more likely to benefit from cord blood
• Survival outcomes comparable to other sources of stem cells
• Use extended in older populations with reduced intensity conditioning and double cord blood transplant
• New results for improving engraftment and immune reconstitution
Problems unique to Cord Blood Transplantation

• Delayed hematopoietic recovery

• In part attributed to relatively low TNC delivered and donor-recipient HLA-mismatch

• Likely to result in longer length of stay

• But GVHD risks are lower which may offer an advantage in terms of costs as well as quality of life
Number of cord blood units worldwide

Total number of cord blood units

610,950 CBUs

Data from BMDW - Bone Marrow Donors Worldwide
Eurocord Registry at ABM
European CBUs shipped by year

Year of shipment | N° of CBUs
--- | ---
1990 | 3
1991 | 1
1992 | 2
1993 | 1
1994 | 5
1995 | 15
1996 | 30
1997 | 58
1998 | 92
1999 | 123
2000 | 143
2001 | 188
2002 | 162
2003 | 187
2004 | 292
2005 | 430
2006 | 570
2007 | 686
2008 | 808
2009 | 811
2010 | 881
2011 | 823
2012 | 860
2013 | 835

N=8081
Eurocord Registry at ABM
Unrelated European CBT by year and recipient’s age
Unrelated European CBT by graft type

Adults

60% double CBT

* Still collecting 2013 data
Single and double UCBT: distribution of age for adult patients

- >60 y: 353 (Eurocord), 477 (CIBMTR)
- 50-59 y: 752 (Eurocord), 805 (CIBMTR)
- 40-49 y: 719 (Eurocord), 790 (CIBMTR)
- 30-39 y: 736 (Eurocord), 780 (CIBMTR)
- 16-30 y: 1103 (Eurocord), 1171 (CIBMTR)

35% adults >50 years
Why UCBT in adults has been increasing over the years and is now a plateau?

- Use of double cord to increase the TNC dose and facilitate engraftment
- Increased confidence in the procedure
  
  Several published reports showed similar outcomes of UCBT with HLA matched bone marrow or peripheral blood stem cell donors
- The use of reduced intensity conditioning (RIC) regimen that decreases the mortality related to transplantation

- **Decreased use in recent years:**
  
  - Competition with related haplo identical HSCT
  - Cost of graft acquisition especially for dUCBT
DUCB HCT: lower risk of Relapse Acute Leukemia in CR1 & CR2

\[ P = .04 \]

31% (19-43)

16% (8-24)
Transplants by diagnosis

Adults

- Acute leukemia: 59%
- MDS /MPD: 14%
- Lymphomas: 3%
- Plasma cell disorders / Solid tumors: 3%
- Bone Marrow Failure Sd: 1%
- Other non malignant disorders: 20%
Single and Double UCBT in EBMT centers, n=2768
Adult, 2-y OS according to disease:

- MDS/MPS: 25±3%; n=380
- Plasma cell disorder: 44±6%; n=94
- Lymphoma: 44±3%; n=329
- Acute leukemia: 38±2%; n=1685
- Chronic leukemia: 40±3%; n=268

p=0.017
How to improve results

• Choice of the cord blood unit
  – Increase cell dose:
    • double cord
    • Ex vivo expansion
    • Improve homing
  – HLA matching

• Conditioning

• Improve immune reconstitution
Impact of allele-level HLA matching on outcomes after myeloablative single unit umbilical cord blood transplantation for hematologic malignancy

Single and Double UCBT in EBMT centers, n=2768
Adult, 2-y OS according to disease:

- MDS/MPS: 25±3%; n=380
- Plasma cell disorder: 44±6%; n=94
- Lymphoma: 44±3%; n=329
- Acute leukemia: 38±2%; n=1685
- Chronic leukemia: 40±3%; n=268

p=0.017
DUCB HCT: lower risk of Relapse Acute Leukemia in CR1 & CR2

Probability

0.0 0.2 0.4 0.6 0.8 1.0

Years

0 1 2 3 4 5

One 84 45 32 27 23 18
Two 93 47 31 23 14 8

P = .04

31% (19-43)
16% (8-24)
Non-relapse Mortality

4/8 HLA-matched (N=254; 37%)
5/8 HLA-matched (N=464; 34%)
6/8 HLA-matched (N=410; 26%)
3/8 HLA-matched (N=85; 41%)
7/8 HLA-matched (N=226; 26%)
8/8 HLA-matched (N=117; 9%)

Eapen M et al, Blood 2014
Neutrophil Recovery

P=0.005

8/8 (71%)
7/8 (62%)
6/8 (66%)
5/8 (58%)
4/8 (56%)
3/8 (53%)

Incidence, %

Days

Eapen M et al, Blood 2014
Non-relapse Mortality
- Total Nucleated Cell Dose -

7/8 HLA-matched, TNC < $3 \times 10^7$/kg (N=33; 45%)

7/8 HLA-matched, TNC > $5 \times 10^7$/kg (N=138; 21%)

7/8 HLA-matched, TNC ≥ $3 - 5 \times 10^7$/kg (N=52; 24%)

Eapen M et al, Blood 2014
Select units with TNC \( \geq 3 \times 10^7/\text{kg} \)

Best HLA match

Allele-level match at HLA-A, -B, -C and -DRB1

Avoid 3/8 HLA-matched transplants

Absence of HLA-C typing match at HLA-B

HLA-C at confirmatory typing

7/8 and 6/8 are better tolerated than 5/8 or 4/8 HLA-matched transplants

TNC in excess of minimum required does not lower NRM
Double Cord blood

- Facilitates engraftment by increasing total cell dose
- Lowers risk of relapse
- Higher GVHD incidence
- Reduced TRM when compared to single-unit historic controls, however some reports showed similar outcomes with the use of sUCBT and dUCBT
- Cost of acquisition of two cord blood and cost-effectiveness of the procedure
DUCB HCT: lower risk of Relapse
Acute Leukemia in CR1 & CR2

P = .04

31% (19-43)
16% (8-24)
2 years- incidence of relapse after sUCBT and dUCBT in adults with AL transplanted in first complete remission (CR1)

In a multivariate analysis adjusted for differences and risk factors
Double CBT was associated with decreased relapse [p=0.01 HR=0.74 (0.58-0.93)]
2 years- incidence of relapse after sUCBT and dUCBT in adults with AL transplanted in first complete remission (CR1)

In a multivariate analysis adjusted for differences and risk factors, Double CBT was associated with decreased relapse [p=0.01 HR=0.74 (0.58-0.93)]

Rocha et al, Eurocord
Acute GVHD after UCB HCT

Single UCB 11% (7-15%)
Double UCB 21% (15-27%)
Double UCB 60% (52-68%)

Median onset

p < .01

MacMillan, 2009

Cumulative Proportion

Days

0.0
0.2
0.4
0.6
0.8
1.0

0 20 40 60 80 100

MacMillan, 2009
Incidence of Chronic GVHD
All Patients

Incidence

Months

Double

Single

p = .12

0.0
0.2
0.4
0.6
0.8
1.0
0
2
4
6
8
10
12
Leukemia-free Survival
Adults over 50   AML in CR1

Probability, %

8/8 URD (N=440)
7/8 URD (N=92)
UCB (N=204)
Benefits of UCB: perhaps best for older patients

- Less Chronic GVHD after UCB
  - Earlier discontinuation of immunosuppression
  - Lesser medical interventions day 100 – 1 year
  - Lesser late morbidity & cost
Outcomes of unrelated cord blood transplant for adults with acute lymphoblastic leukemia: a survey conducted by Eurocord and the ALWP/EBMT

L Tucunduva, A Ruggeri, G Sanz, S Furst, B Rio, G Socié, W Arcese, M Michallet, I Yakoub-Agha, J Cornelissen, J Sanz, P Montesinos, D Purtill, E Gluckman, M Mohty and V Rocha

39th EBMT Annual Meeting
London, April 9th 2013

No conflict of interest to disclose
Results - 2y LFS all patients

- CR1: 39±4% (n=195)
- CR2: 31±4% (n=136)
- Not in CR: 8±3% (n=90)

p<0.0001
Results - 3y LFS according to MRD status at UCBT

- MRD negative: 49±8% (n=58)
- MRD positive: 28±6% (n=39)

p=0.062
Conditioning regimen in UCBT

**MAC** (single or double units)

**TBI 12 GY + CY**

**BU + CY + Fludarabine (120-150mg/m2) + ATG**

**TBF:** Thiopeta + BU + Fludarabine + ATG

**RIC** (single or double units)

**TCF:** TBI 2 Gy + CY + Fludarabine ± ATG
Comparison of outcomes after single or double cord blood transplantation in adults with acute leukemia using different types of myeloablative conditioning regimen in remission - a retrospective study

Annalisa Ruggeri, Guillermo Sanz, Henrique Bittencourt Alessandro Rambaldi, Ibrahim Yakoub-Agha, Jose Ribeira, William Arcese, Lionel Mannone, Jorge Sierra, Carlos Solano, Samir Nabhan, Luciana Tucunduva, Fernanda Volt, Chantal Kenzey, Eliane Gluckman, Myriam Labopin, Vanderson Rocha on behalf of Eurocord and the Acute Leukemia Working Party of EBMT.

Leukemia 2013

No conflict of interest to disclose
Relapse at 2-year-MAC sUCBT and dUCBT in adults with AL in CR1

CI of relapse: $19 \pm 3\%$

Group 1: sUCBT-CyTBI12/BU: $25 \pm 4\%$, $n=68$

Group 2: sUCBT-TBF+ATG: $18 \pm 3\%$, $n=88$

Group 3: dUCBT-CyFluTBI12: $16 \pm 3\%$, $n=83$

No factors associated with RI in the multivariate analysis.
LFS at 2-year-MAC sUCBT and dUCBT in adults with AL in CR1

Group 1: sUCBT-CyTBI12: 30±7%, n=68
Group 2: sUCBT-TBF+ATG: 46±6%, n=88
Group 3: dUCBT-CyFluTBI12/BU: 48±6%, n=83

p=0.03
Results - 2y LFS after UCBT for adults with ALL

- no ATG 39±6% (n=72)
- ATG 23±3% (n=212)

p=0.02

Tucunduva L et al, BMT in press
MAC setting in malignant diseases

- In Adults with AL

TBI+CY+Flu without ATG using double cord blood transplants and TBF+ATG using single units have similar results
Which is the “best” RIC for UCBT?
Treatment-Related Mortality

Cumulative Incidence, %

- dCB other vs. dCB TCF ± ATG: 2.96 (1.61 – 5.45), p < 0.0001
- MMUD vs. dCB TCF ± ATG: 1.77 (1.04 – 2.99), p = 0.035
- MUD vs. dCB other: 0.37 (0.18 – 0.62), p = 0.0001

Cumulative Incidence:
- dCB, other: 52%
- MMUD: 30%
- MUD: 23%
- dCB, TCF: 22%
Leukemia-Free Survival

MUD vs. dCB other: $0.68 (0.47 - 0.99)$, $0.046$

- MUD: 31%
- MMUD: 25%
- dCB, TCF: 26%
- dCB, other: 9%
Alternative donor hematopoietic stem cell transplantation for mature lymphoid malignancies after reduced-intensity conditioning regimen: similar outcomes with umbilical cord blood and unrelated donor peripheral blood

DUCB HCT: lower risk of Relapse Acute Leukemia in CR1 & CR2

31% (19-43)

16% (8-24)

$P = .04$
Rodrigues C et al, 2013

UCBT = 104

75% TCF

PB = 541

29%

28%

Probability of CS

0% 20% 40% 60% 80% 100%

Months

UCBT = 104

56%

PB = 541

49%

Probability of CS

0% 20% 40% 60% 80% 100%

Months

Eurocord - International Registry on Cord Blood Transplantation
Conclusion - Summary

• Results of single and double UCBT are similar for patients with acute leukemia, supporting the use of dUCBT when a single UCB unit (TNC dose (>2.5x10^7/Kg)) is not available.

• In the MAC setting, a single UCBT with adequate TNC using TBF gives same results as double UCBT.

• As for cost-effectiveness between single and double UCBT, data from France suggests that, in both MAC and RIC settings, dUCBT is associated with better outcomes and is more cost-effective strategy for adult pts with acute leukemia.

• However, costs vary according to countries and the cost-effectiveness of the procedures needs to be evaluated in the specific context where the UCBT is performed.
### UCBT

#### Pros
- CB banks: ~600,000 units, immediate availability, no donor risk, advantage for ethnic minorities, low risk of transmissible infections
- Applicability for children and adults with malignant and non malignant disorders
- Survival outcomes comparable to other sources of HSCs
- HLA mismatch accepted; ↓ GvHD and relapse (> GvL)
- Use extended in older populations with RIC and double UCBT

#### Cons
- Delayed engraftment and immune reconstitution; high risk of graft failure (> TRM)
- Unavailability of the donor for additional donations (i.e DLI)
- Sustainability of CB banks

### Critical issue in UCB unit selection: CELL DOSE
- TNC dose ≥ 2.5x10^7/kg (≥ 4 in non malignant)
- 0-1 MM better than 2, avoid 3-4 MM
- higher cell dose allows > HLA mismatches
Conclusion

Multiple factors involved in the donor and HSCs source choice

- Patient’s & Disease’s features
- Donor’s safety & features
- Transplant setting
- Centre
  Clinical Approach & Expertise

The wide choice of donor sources has extended the possibility of offering HSCT to *almost all* patients who need this procedure.
Criteria of CB unit choice - EUROCORD

- Look at the number of cells in MAC, RIC:
  - >2.5x10^7 NC/kg and or >1x10^5 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:
  - Malignant diseases: cell dose is the best prognostic factor because HLA differences reduce relapse (GVL)
  - Non malignant diseases: increase cell dose (>4.0x10^7 NC/kg ) and find the best HLA match
  - If the minimum number of cells for a single UCBT is not achieved, a double UCBT should be considered

- Other considerations, if several CBU are available consider:
  - Cord Blood Bank accreditation status and location
  - ABO compatibility
  - NIMA and KIR status