Selection of the Optimal Umbilical Cord Blood Unit

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OUTLINE

- Cell Dose
- HLA Match
  - Allele Level
  - HLA C
  - KIR
  - Directional Mismatch
  - NIMA
- HLA Antibodies
- Racial/Ethnic Match
- Cord Blood Banking Techniques
CASE PRESENTATION

- AL 35 year old woman
- 2009 Fatigue, Heavy Menses, Low counts
- Bone marrow: Acute Myeloid Leukemia, normal cytogenetics, NPM1+, Flt3 ITD and D835-, novelflt3 3 base pair insertion
- Treated on US Intergroup protocol-Induction Daunorubicin/Cytarabine-Complete Remission
- Received Autologous SCT 2010 and post SCT Decitabine per protocol
- Relapsed 4/2012- flt 3 ITD +
- Treated with High Dose Cytarabine-CR
CASE PRESENTATION

- No Matched related or unrelated donor
- Protocol - Fludara/Melphalan/low dose TBI
- On post transplant Sorafenib on protocol
- Course Complicated by HHV-6 reactivation, Strep mitus bacteremia, prolonged nausea, diarrhea
- Colon biopsy—no GVHD/infection? Cord colitis
- Intermittent improvement on Flagyl/Ciprofloxocin
- In Complete Remission, PS 0, Back to work and her garden, 1 year post transplant
BACKGROUND

- Initial transplants in children, extended to adults
- Over 30,000 UCB transplants performed worldwide
- Over 500,000 UCB donated to public storage banks
- 43 Banks in 28 countries
Figure 1

a. Children in Europe
   - 2006-2011
   - 2000-2005
   - 1996-1999

b. Children in North America
   - 2006-2011
   - 2000-2005
   - 1996-1999

Children in Europe

Children in North America

Adults in Europe

Adults in North America

Courtesy of Dr. Gluckman
ADVANTAGES OF CORD BLOOD

- No Risk to Mother or Baby
  No operating room or pheresis
- Readily Available
  No Need to Recontact Donor
- Less Risk of Graft vs Host Disease
- Possibly Lower Relapse Rate
- Opportunity for Larger, Diverse Group of Donors
CORD BLOOD:
CRITICAL CONCERNS

- One-time donation
  No opportunity for Donor Lymphocyte Infusion
- Cost—US $30,000-$45,000/unit
- Cell dose important factor for engraftment
  Average size banked unit 120 x 10 (7) NC
- Average need for transplant >3.0 10 (7) NC/kg
- Only fraction of UCB units sufficient cell dose for adults/heavier children
- US 10kg heavier than in Europe, 15 kg heavier than in Asia
- Higher Risk of Infection and Poor Immune Recovery after Cord Blood Transplant
STRATEGIES to ADDRESS CRITICAL CONCERNS

- Expansion of Cord Blood Units
  Prostaglandin/Notch/Angioblast
- Pooling of Cord Blood Units
  Double Cord
  Cord Blood plus Haplo Transplant
- Patient Selection
  Improved Infection Prevention/Immune Recovery
- Selection of the Optimal Cord Blood Unit
  May be a Controllable Factor
  Cell Dose, HLA Match
  Banking and Other Factors
"You're fifty-seven years old. I'd like to get that down a bit."
SINGLE VS DOUBLE CORD BLOOD TRANSPLANT

- **Single Cord Blood Transplantation**
  - Used more commonly in pediatrics, less expensive
  - Pediatric randomized CTN study of single vs. double

- **Double Cord Blood Transplantation**
  - More popular in US — population 10 kg heavier than in Europe, 15 kg heavier than in Asia
  - Preliminary Data — decreased relapse with 2 units but more GVHD
  - Engraftment quicker although immune recovery still an issue
Disease-free Survival
- Intent-to-Treat -

Number at risk

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<th>Months</th>
<th>Double UCB</th>
<th>Single UCB</th>
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<tr>
<td>0</td>
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<td>113</td>
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Double UCB: 64% (54 – 72)
Single UCB: 68% (58 – 76)

P=0.22

Wagner et al. ASH 2012
Neutrophil Recovery
- Transplanted -

Single UCB @ Day 42: 89% (83 – 95)

Double UCB @ day 42: 86% (80 - 93)

P=0.08
CONCLUSIONS

- Disease Free Survival 66% Entire Cohort
- Disease Free Survival, Overall Survival, Non Relapse Mortality, Relapse and Neutrophil Recovery Similar Between Single and Double UCBT
- Grade III-IV GVHD Higher in Double UCBT
- Lower Incidence of Platelet Recovery in Double UCBT
- Single UCBT Standard of Care in Pediatric Patients
- Double UCBT Only if No Adequate Single Cord
RIC sUCBT versus dUCBT for adults with AL in CR1
2-year CI of Chronic GVHD

\[ \text{dUCBT, n=136} \quad 21 \pm 4\% \\
\text{sUCBT, n=76} \quad 12 \pm 5\% \]

Rocha et al, ASH 2012
RIC sUCBT versus dUCBT for adults with AL in CR1
2 years Relapse incidence

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- LFS after RIC sUCBT and dUCBT in adults with AL in CR1

In a multivariate analysis adjusted for differences and risk factors Double CBT was associated with improved LFS rates [p=0.04 HR=0.64 (0.41-0.99)]
2 years- LFS after RIC sUCBT and dUCBT in adults with AL in CR2, n=148

![Graph showing LFS over time for sUCBT and dUCBT.](image)

- sUCBT, n=55: 48 ± 3%
- dUCBT, n=93: 40 ± 6%
CONCLUSIONS

- Acute Leukemia in CR 1
  - Double Cord Decreased Relapse
  - Double Cord Improved LFS
- Acute Leukemia in CR 2
  - Single and Double Cord Similar Outcomes
- Suggests More Potent Graft vs Leukemia Effect in Less Advanced Disease
- Children-No Advantage to Double Cord
- Adults-Further Investigation Needed
Selection of Optimal Cord Blood Unit Cell Dose and HLA

- Combined effect of HLA and Cell Dose
- 1061 single, myeloablative-leukemia/MDS
  - 6/6 match lowest TRM, regardless of cell dose
  - 1 mismatch $2.5 \times 10^7$ equal to 1 or 2 mismatch with $>5 \times 10^7$
  - 2 mismatch 2.5-5.0 had greater TRM
  - 1 or 2 mismatch $< 2.5$ poor outcome
- Increased risk of GVHD with higher mismatch
- No decrease in relapse with higher mismatch

Barker et al Blood 2010
Double CB: Cell Dose and HLA

- 84 Double CB recipients
- Higher CD3+ and CD34+ cell viability associated with unit dominance
- Dominant unit higher TNC, CD34+ associated with faster engraftment
- High resolution HLA disparity no effect on engraftment
- CB unit to unit HLA match no effect on engraftment

Avery et al Blood 2011
High Resolution HLA Typing

- Boston approach, Double Cord, Reduced Intensity, Require Allele Level Typing
- Cord Blood Units 4/6 or better allele level match with patient and with each other
- Neutrophil ($p=0.006$) and platelet ($p=0.033$) engraftment faster if HLA-B matched
- HLA DR matching lower risk of GVHD in patients treated with Cya/MMF
- HLA match no effect on OS or DFS
- HLA match did not affect cord unit predominance

Delaney et al Transfusion, 2008
HLA Disparity in GVHD Direction

- 152 single cord, myeloablative patients
  - HLA mismatch in the GVHD direction associated with longer time to engraftment
  - HLA mismatch in the host vs graft direction no effect on engraftment
  - HLA disparity no effect on survival

- EBMT/Eurocord study of 1565 patients
  - 1 or 2 HLA mismatches in either direction no impact on survival

- Japanese study of 2977 patients
  - Direction of mismatch no impact on survival

Cunha et al BMT 2013
Matsuno et al Blood 2009
Kanda et al BBMT 2013
HLA C Matching

- 803 patients, single CB, myeloablative regimen
- 69% under age 16
- Typing at HLA A, B, C (intermediate level) DR (allele level)
- Higher TRM if mismatch at HLA-C compared to fully matched at A, B, C, DR
- Higher TRM is 1 mismatch at HLA A, B, DR and mismatch at HLA C compared to 1 mismatch at HLA A, B, DR
- No increase in TRM if mismatched at 2, 3, or 4 loci

Eapen et al Lancet Oncology 2012
Non Inherited Maternal Allele

- 1121 single myeloablative CB transplants
  - 79 patients had mismatched antigen identical to donor NIMA
  - TRM decreased in NIMA, especially > 10 years old

- Matched pair analysis of 48 NIMA matched UCBT and 116 non NIMA matched
  - 5 year OS higher in NIMA matched, 55% vs 38%, p=-.04

Rocha et al BBMT 2012
Van Rood et al PNAS 2009
KIR Typing

- Conflicting results in MUD and CB transplants
- 257 double or single cord blood patients
- Myeloablative conditioning (155 patients)
  - KIR-L mismatch no effect on GVHD, TRM, relapse or survival
- Reduced intensity conditioning (102 patients)
  - KIR-L mismatch increased GVHD, risk of death

Brunstein et al Blood 2009
386 myeloablative single CB, median age 33
- 89 patients with HLA antibodies, more likely older, women
20 patients with HLA antibody vs CB HLA (15 Class I and 5 Class 2)

Incidence ANC recovery at Day 60
- 83% Ab negative, 32% Ab+ vs cord

Incidence platelet recovery at Day 90
- 72% Ab negative, 33% Ab+ vs cord

HLA Antibody no effect on GVHD, relapse, TRM

EFS at 2 years
- 43% Ab negative, 15% Ab+ vs cord, p=0.0001

Takanashi Blood 2010
Donor Specific HLA Antibodies on UCB Unit Selection: Double Cord

- 73 patients, ≥4/6 allele level match
- Double UCBT, RIC
- 22% patients HLA antibody vs 1 or 2 UCB
- HLA Ab increased risk of graft failure:
  - 5% no HLA Ab, 18% HLA Ab vs 1 UCB, 57% HLA Ab vs 2 UCB
- HLA Ab vs both UCB units associated with worse survival, 45% vs 0, p=0.04

Cutler et al, Blood 2011
Racial/Ethnic Match

• CIBMTR Study, Single Cord, 885 Patients
  ➢ African American patients worse OS than Hispanic or Caucasian patients
  ➢ African Americans received smaller, less well matched units
  ➢ Race/Ethnicity of Cord Blood Donor no Impact on Survival

• Minnesota Study
  ➢ 475 double and single cord blood patients
  ➢ Donor race matching did not affect survival

Ustun et al Leuk Lymphoma 2013
Ballen et al BBMT 2012
Cord Blood Bank of Origin

- No Study to Show One CB Bank Better than Another
- Many Centers Prefer their own Domestic Banks
- In Utero and Ex Utero Collection Similar Cell Counts
- Extensive Variability in Cord Blood Unit “Quality”
- Large CIBMTR Study Underway to Correlate CB Bank of Origin, Processing, and Thawing Techniques with Transplant Outcomes

Scaradavou et al BBMT 2010
Laskey et al Transfusion 2002
Mass General/DFCI/BIDMC
Approach to Cord Blood Selection

- **Selection Criteria:**
  - Combined cell dose >$3.7 \times 10^7$NC/kg, each cord >$1.5 \times 10^7$NC/kg
  - ≥4/6 Allele Level Match at A,B, and DR with patient and each other
  - Cell dose priority over HLA match
  - HLA Antibody an exclusion

- **Not used for Selection**
  - NIMA
  - HLA C-under review
  - KIR
  - Race/Ethnicity
  - Bank of Origin/Licensure
CONCLUSIONS

- Significant Growth of Cord Blood Banking and Transplantation
- Improved Outcomes for Children and Adults
- First Randomized Study of UCB vs Haplo Underway
- “Low Hanging Fruit”-Cord Blood Selection
- Cell Dose, HLA Important
- HLA C likely to be important Factor
- HLA Antibodies negative effect
- Unknown: Allele level typing, degree of mismatch, KIR, ethnicity, banking techniques
FUTURE OF CORD BLOOD TRANSPLANTATION

- Better UCB selection techniques
  - KIR, high resolution typing, HLA C, NIMA
- Ex vivo expansion techniques
  - Notch, Angioblast, PGE2
- Immune recovery and infection
  - Cytotoxic T lymphocytes, strategies to reduce ATG or add rituximab
- Increased utilization and demand, cost will decrease