Umbilical Cord Blood: An Alternative Allogeneic Stem Cell Source for Transplantation

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Allogeneic Stem Cell Transplantation in AML

Over the past 3 decades allogeneic transplantation has been established as an effective salvage treatment for relapsed and high risk AML. The alloreactive immunotherapeutic effects, termed ‘GVL’ contribute greatly to its efficacy. No other established therapy exerts as strong an anti-leukemic effect. Unfortunately wide application of alloSCT is limited by graft availability and is considerably offset in the unrelated setting by complications related to disparity of donor-recipient histocompatibility contributing to Graft vs. Host Disease, which exerts a significant price in mortality and morbidity. As a result, alloSCT produces only a limited gain in AML survival in the unrelated setting despite significantly reducing relapse.
Overview: UCB Transplant

- Allogeneic transplantation for hematology patients is limited by graft availability.

- UCB is a new alternative graft source; to date approximately 8000 procedures have been performed worldwide.

- Application of UCB transplantation has previously been limited by low cell dose, particularly in adult patients.
Overview: UCB Transplant

Continued

• Two large retrospective European and American studies reported in 2004 comparing transplant outcomes with URD vs. UCB indicate equivalence in adult leukemia patients.

• Current studies are focused on UCB graft engineering and immune reconstitution in acute leukemia patients.
Clinical Problem
Allogeneic Graft Availability

Hematology Patients Needing BMT

- Only 20-35% Receive BMT via Adult Registry Match
- No Compatible Family Donor
- Compatible Sibling Donor

8/10

2/10

Only 20-35% Receive BMT via Adult Registry Match
UCB Stem Cells

Advantages

• Abundantly available / birthing represents genetic background of any population.

• Harvested at no risk to mother or infant.

• Easily shipped frozen to transplant center, quickly available for patients with unstable disease.

• Lymphocyte immune tolerance of the neonate with low Th1 associated cytokine production.

• Non-controversial source of post-natal stem cells.

• No malignant transformation after infusion.
UCB Stem Cells

Disadvantages

• One time donation with finite volume.

• Prolonged kinetics hematopoietic engraftment.

• Limited graft cell dose in adult recipients.
Pioneers in UCB

- 1988 proof of concept: first related UCB transplant into a 5 year old child with Fanconi anemia. This patient remains alive and disease free.

- Subsequent contributions to the UCB field included analyses of engraftment, GVHD, GVL and immune reconstitution in pediatric and adult hematology patients.

E. Gluckman, MD
Hospital Saint Louis, Paris
UCB Transplant

• The acute leukemia working party of the EBMT/Eurocord-Netcord registry compared outcomes in 682 adult leukemia patients for whom 98 received UCB and 584 BM from URD during 1998-2002.

• Multivariate analysis showed UCB yielded lower risks of aGVHD and slower neutrophil recovery.

• The incidence of cGVHD, TRM, relapse and LFS did not differ comparing UCB and URD.
LFS after Cord Blood or Bone Marrow Transplant from Unrelated Donors in Adults

Pioneers in UCB

- Developed UCB collection and cryopreservation protocols.

- Established first related UCB registry in collaboration with EBMT and reported results in 44 pediatric hematology patients.*

- Subsequent contributions included UCB graft analyses as predictors of engraftment / survival and use of dual UCB grafts.


J. Wagner, MD
University of Minnesota
Survival after 0-3 mismatched unrelated UCBT & 6/6 HLA-matched BMT in children

Patient analyses with match for age, diagnosis, and disease stage.

Graft Cell Dose is a Critical Determinant of TRM after Single Unit UCBT (n = 102)

TRM by CD34+ dose (x 10^5/kg)

70% survival at 1 year if unit > 1.7 x 10^5 CD34+/kg.

DFS for Acute Leukemia in CR
Single vs. Double UCBT
CY60/TBI1320

Double: Adults + Adolescents
Single: Children

Cumulative Proportion vs. Months

Double line
Single line

Months: 0 2 4 6 8 10 12
Cumulative Proportion: 1.0 0.8 0.6 0.4 0.2 0.0
Pioneers in UCB

- Developed the National Cord Blood Program, the first cord blood bank for unrelated recipients.
- Currently the largest public bank world-wide (45,000 units donated with 2,300-plus patients transplanted; including >800 adults).
- NCBP has developed and maintains the most extensive database on UCB transplantation outcomes world-wide.

P. Rubinstein, MD, C. Stevens, MD
National Cord Blood Program
New York Blood Center
UCB ANC recovery by cell dose

UCB Transplantation
Unrelated Donors/562 Patients

Genetic Diseases 24%
Acquired Diseases 8%
Leukemia/Lymphoma 67%

PROBABILITY OF SURVIVAL
Impact of Cell dose and HLA mismatch
Pioneers in UCB

- Proof of concept: performed first unrelated UCB transplant in 1993.
- Subsequent contributions have included analyses of UCB engraftment, GVHD, survival, and immune reconstitution in pediatric and adult hematology patients.
- Focused studies of UCB transplantation in children with inherited metabolic diseases; Hurler’s syndrome and Krabbe’s disease.
Cumulative Incidence of Neutrophil and Platelet Engraftment and EFS in Hurler’s Disease after Cord-Blood Transplant

Probability of Survival in Krabbe's Disease after UCB Transplant

Clinical Reports: UCB in Adults

• UCB as a novel stem cell source in pediatric recipients with noted delayed hematologic engraftment and reduced GVHD compared with conventional stem cell grafts.

• The focus of our initial study was to determine the feasibility of UCB transplant in adults. Outcomes in 68 adults treated consecutively at 5 US centers during the time period 2/95 to 9/99 were analyzed.

Probability of neutrophil recovery by UCB graft cell dose level

Probability of event free survival by graft CD34 infused cell dose

Probability of event free survival by graft CD34 infused cell dose.

UCB Graft Engineering Strategies

**Cytokine-based UCB expansion.**

hypotheses: Engraftment \(?\) Faster and/or improved survival than non-expanded UCB.

![Day 0](#) ![Day 12](#)  

J. Jarosck \(\text{Blood}\) 2003.  
E.J. Shpall \(\text{Biol Blood Marrow Transplant}\) 2002.

**Infusion of dual UCB units.**

hypotheses:  
1. \(?\) Graft vs. graft immuno-reactivity.  
2. Kinetics of engraftment.

Pioneers in UCB

- J. Barker has reported on 23 patients infused with 2 UCB units (median total dose cryopreserved 3.5x10^7/kg) after ablative conditioning in whom all evaluable patients demonstrated sustained donor engraftment.

- Chimerism revealed emergence of one donor over time. Neither cell dose nor HLA was predictive for engraftment.

- GVHD incidence paralleled that of historic controls.

- One year EFS was 57% overall and 72% in patients transplanted in CR.

J. Barker, MD
Memorial Sloan Kettering Cancer Center

Unrelated Donor Search Time

**Start of Formal Search**

**BM**

- 19 days (1-257)
- 30 days (10-101)
- 50 days (32-293) (N = 58)

**UCB**

- 13.5 days (2-387) (N = 50)

**UCB availability significantly faster than BM**


- Donor identified
- Donor available
Sustained Donor Engraftment

Cy/Flu/TBI (n = 22)
9.5 days (5-28)
94% (95% CI: 84-100)

Bu/Flu/TBI (n = 21)
26 days (12-30)
76% (95% CI: 56-96)

$p < 0.01$

Cy/Flu/TBI is non-myeloablative & engraftment is superior to Bu/Flu/TBI

Regression of relapsed or persistent disease (n = 16) suggest a GVM effect & better PFS in specific disease groups (e.g. indolent NHL/CLL/mantle cell NHL CR in 12/16)

Barker et al: Blood 2004, 104; 235a
Pioneers in UCB

• Dr. Shpall reported in 37 patients (25 adults/12 children) that augmentation of UCB with ex vivo expanded cells resulted in engraftment in all evaluable patients with median 28 days to ANC500.

• Survival at 30 months was 35%.

E.J. Shpall, MD
MD Anderson Cancer Center

Shpall E.J. *et al.* Biol Blood Marrow Transplant (2002); 8 (7): 368-76.
### Ex Vivo Expansion of Cord Blood

University of Colorado Trial

<table>
<thead>
<tr>
<th>Cords in 2 Fractions:</th>
<th>Expanded 40%, 60% Fractions</th>
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</thead>
<tbody>
<tr>
<td>CD34 Selection:</td>
<td>Isolex 300i</td>
</tr>
<tr>
<td>Cell Density:</td>
<td>(\sim 1 \times 10^6) CD34+ cells in 800 ml</td>
</tr>
<tr>
<td>Growth Factors:</td>
<td>SCF, G-CSF, MGDF 100 ng/ml</td>
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<tr>
<td>Culture Medium:</td>
<td>Amgen defined media</td>
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<tr>
<td>Culture Bags:</td>
<td>1L Teflon bags, Am. Fluoroseal</td>
</tr>
<tr>
<td>Culture Duration:</td>
<td>10 Days</td>
</tr>
</tbody>
</table>

- **Engraftment failure rate low** (2/33 = 6%)
- **Engraftment rates in range of recipients of higher cell doses:** neutrophils 35, platelets 300 days

Shpall E.J. *et al.* Biol Blood Marrow Transplant (2002); 8 (7): 368-76.
MDACC Protocol # 02-407: Double vs. Expanded Cord
IND #7166 (MD Anderson Sponsor)

Patients with Hematologic Malignancies
Randomize (30 per arm)

Primary Endpoints:
• Time to neutrophil engraftment
• Engraftment failure

Two Unmanipulated Cords
One Expanded and One Unmanipulated Cord

Immune Reconstitution (Komanduri Laboratory):
• T and NK subsets
• TREC assays
• Functional T Cell Recovery (CFC assays)
Dr. Shpall has lead the study group in FACT to establish FACT standards for UCB banking.

An initial nine cord blood banks accredited located in New York, North Carolina, Belgium, France, Spain, Germany, United Kingdom, Finland and Italy were the first to earn FACT-NETCORD accreditation.

Presently, the FACT-NETCORD Cord Blood Bank Inspection and Accreditation Program has accredited over 40 cord blood banks in 14 countries.
UCB Collection/Processing
Pioneers in UCB

- CIBMTR comparison of transplant outcomes after URD vs. UCB in children and adults with leukemia.

- Analyses UCB graft characteristics and engraftment with large multi-institutional datasets.

M. Horowitz, MD
CIBMTR
University of Wisconsin
The graph illustrates the probability of neutrophil recovery over days for different types of transplants:

- **Bone marrow, matched**: The recovery rates are high and occur within the first 20 days, with most patients recovering within 40 days. The number at risk decreases as recovery progresses.
- **Bone marrow, mismatched**: Recovery rates are lower compared to matched bone marrow, with most patients taking longer to recover, up to 80 days. The number at risk decreases gradually.
- **Cord blood, mismatched**: The recovery rates are the lowest, with recovery times extending to 100 days. The number at risk decreases significantly after the first 20 days.

The table provides a summary of the number at risk for each group:

<table>
<thead>
<tr>
<th>Group</th>
<th>Days 9</th>
<th>Days 3</th>
<th>Days 1</th>
<th>Days 0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone marrow, matched</td>
<td>364</td>
<td>158</td>
<td>9</td>
<td>3</td>
</tr>
<tr>
<td>Bone marrow, mismatched</td>
<td>83</td>
<td>48</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Cord blood, mismatched</td>
<td>147</td>
<td>112</td>
<td>22</td>
<td>7</td>
</tr>
</tbody>
</table>

The graph visually represents the data, showing the percentage of patients who have recovered neutrophils at various time points.
IBMTR UCB vs. URD

- Adult leukemia patients receiving UCB HLA mismatched at one Ag (34 pts), or two Ag (116 pts) were compared with those receiving HLA matched marrow (367 pts) or one Ag mismatched (83 pts).

- Acute GVHD incidence was higher after URD while cGVHD was higher after UCB.

- HLA matched URD was associated with lower TRM and higher survival. One HLA Ag mismatched URD outcomes were equivalent to two Ag mismatched UCB.
Summary

- Current medical therapy for AML is limited by high recurrence rates.
- Allogeneic transplantation is curative in 45-55% high risk AML.
- Application of Allogeneic Transplantation is limited by availability of HLA matched hematopoietic stem cell grafts.
- UCB has emerged as an alternative source of hematopoietic stem cells for transplantation.
- UCB graft immune reactivity differs from hematopoietic stem cell grafts from adult donors, allowing successful transplantation despite HLA disparity.
- Current obstacles to optimal UCB curative potential include engraftment and infection.
- Future studies are focused on UCB stem cell homing and engraftment and immune reconstitution.
Collaborators Case Western Reserve

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