

2014 BMT Pharmacists Conference: Debate - Haploidentical vs. Umbilical Cord Blood Transplant

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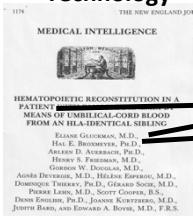
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LMBSTA

Objectives

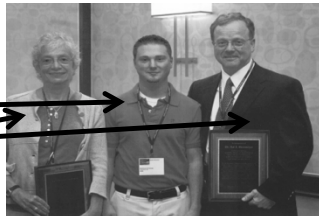
- Defend the selection of patients for umbilical cord blood (UCB) grafts.
- Review outcomes in patients who received reduced-intensity conditioning for UCB transplantation.

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Cord Blood is Relatively Recent Technology



20th anniversary first cord blood transplant (2008)



Eliane Gluckman, MD
Hopital St. Louis, Paris

Matthew Farrow,
recipient
First cord blood transplant

Hal Broxmeyer, PhD
Indiana University
School of Medicine

Obtaining Cord Blood



Courtesy of Dr. Mary Laughlin, University of Virginia

Mismatched Cord Blood

Advantages

- UCB units are rapidly available
- HLA matching is less frequently a barrier to finding a donor
- Risk of acute and chronic GVHD is low in the presence of HLA mismatch
- transmission
- No risk for the donor

Limitations

- Relatively limited repository
- No donor lymphocytes
- Delayed engraftment
- Fixed cell dose
- Cost
- Growing regulatory complexity

Cord Blood Selection

Cryopreserved nucleated cell dose 2.5-3.0 x 10e7/kg

HLA DRB1 at allele level
HLA A and B at antigen level

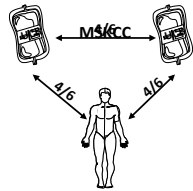
Two Approaches

Select the unit with highest cell dose regardless of the HLA-matching

After a certain cell dose select the best HLA-matched unit

The Double Cord MN Style

If no single graft is big enough then ...



- HLA-match**
- 6/6 $\geq 3.0 \times 10^7$ /kg
 - 5/6 $\geq 4.0 \times 10^7$ /kg
 - 4/6 $\geq 5.0 \times 10^7$ /kg

• Boston combined cell dose 2.7 and allele level A, B and DRB1
 • Combined cell dose $\geq 3.0 \times 10^7$ /kg
 HLA DRB1: Allele level

Cord Blood Selection

Cryopreserved nucleated
cell dose 2.5-3.0 x 10⁷/kg

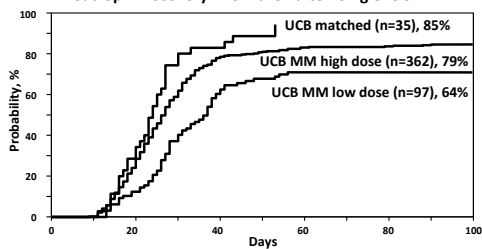
HLA DRB1 at allele level
HLA A and B at antigen level

Tie Breakers

- CD34 cell dose
- High resolution HLA matching
- Matching at HLA-C
- Direction of mismatch
- Mismatching Kir-ligand
- Non-inherited maternal allele
- Anti-HLA antibodies
- Experience with the cord blood bank
- Red cell depleted
- Licensed vs unlicensed cord blood

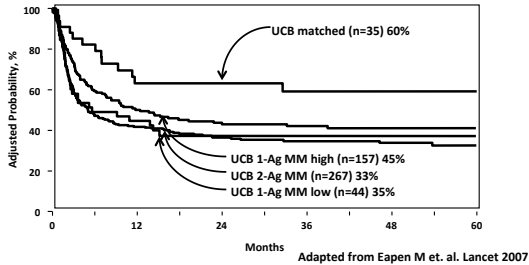
How important is to use well HLA-matched cord blood units?

Neutrophil recovery in Children after Single UCBT



Adapted from Eapen et. al. Lancet 2007

After adjusting for disease status at transplantation, leukemia-free survival was Better for HLA-Matched UCB



keep in mind:

HLA-matching and cell dose are tied to each other and the goal is to use a large, well matched, cord blood unit.

In adults, it is easier said than done.



If high resolution seems to have some influence in outcomes, should we be considering matching at HLA-C locus (like in unrelated adult volunteer donors) when selecting UCB Units?

Treatment Related Mortality

Zero, single, or multiple loci mismatches

A, B, C, and DRB1 match	6/69	1.00	..
One locus (A, B, C, or DRB1) mismatch	27/147	2.02 (0.83–4.91)	0.12
Two loci (A, B, C, or DRB1) mismatch	75/259	3.27 (1.42–7.54)	0.006
Three loci (A, B, C, or DRB1) mismatch	83/253	3.34 (1.45–7.71)	0.005
Four loci (A, B, C, and DRB1) mismatch	28/75	3.51 (1.44–8.58)	0.006



Eapen et al. Lancet Oncology 2011



If better "conventional" HLA-matching matters, should we consider high resolution HLA-matching at A, B and DRB1 when selecting cord blood units?

Results of the Cord Blood Transplantation Study (COBLT): clinical outcomes of unrelated donor umbilical cord blood transplantation in pediatric patients with hematologic malignancies

Joanne Kurtzberg,¹ Vinod K. Prasad,¹ Shelly L. Carter,² John E. Wagner,³ Lee Ann Baxter-Lowe,⁴ Donna Wall,⁵ Neena Kapoor,⁶ Eva C. Guinan,⁷ Stephen A. Feig,⁸ Elizabeth L. Wagner,⁹ and Nancy A. Kernan,¹⁰ on behalf of the COBLT Steering Committee

Total HLA matches	Original HLA match (N = 191)		Final HLA match (N = 179)	
	N	%	N	%
6	17	8.9	16	8.9
5	58	30.4	40	22.3
4	111	58.1	77	43.0
3	5	2.6	35	19.6
2	0	0	11	6.1

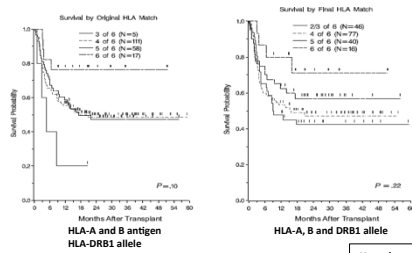
HLA-A and B antigen
HLA-DRB1 allele

HLA-A, B and DRB1 allele
Kurtzberg et al Blood 2008



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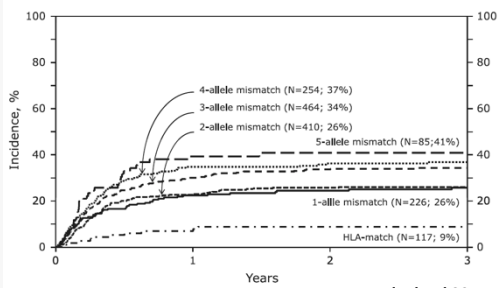
HLA-A and B antigen
HLA-DRB1 allele

HLA-A, B and DRB1 allele

Kurtzberg et al Blood 2008



Effect of High Resolution HLA Matching on Outcomes of Single UCB Transplantation

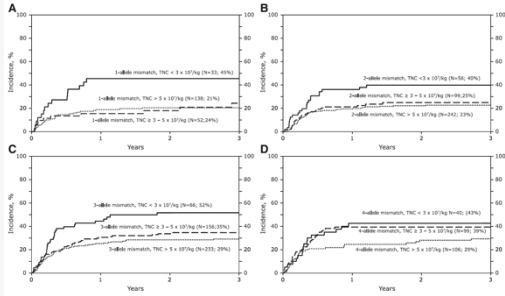


Eapen et al. Blood 2014

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Effect of High Resolution HLA Matching on Outcomes of Single UCB Transplantation



Eapen et al. Blood 2014

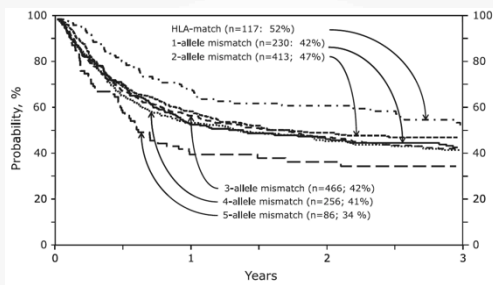
Effect of High Resolution HLA Matching on Outcomes of Single UCB Transplantation

Relapse

1-allele mismatched vs matched	226 vs 117	0.93 (0.65-1.33)	.69
2-allele mismatched vs matched	410 vs 117	0.77 (0.55-1.07)	.12
3-allele mismatched vs matched	464 vs 117	0.75 (0.53-1.05)	.09
4-allele mismatched vs matched	254 vs 117	0.50 (0.33-0.73)	.001
5-allele mismatched vs matched	84 vs 117	0.83 (0.50-1.36)	.45
3-4 allele vs 1-2 allele mismatched	718 vs 637	0.78 (0.64-0.96)	.02
5 allele vs 1-2 allele mismatched	85 vs 637	1.01 (0.66-1.54)	.98
5 allele vs 3-4 allele mismatched	85 vs 718	1.28 (0.84-1.97)	.25

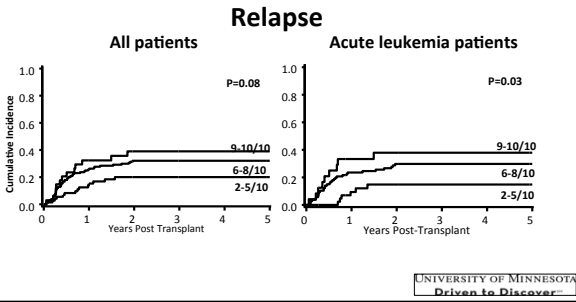
Eapen et al. Blood 2014

Effect of High Resolution HLA Matching on Outcomes of Single UCB Transplantation

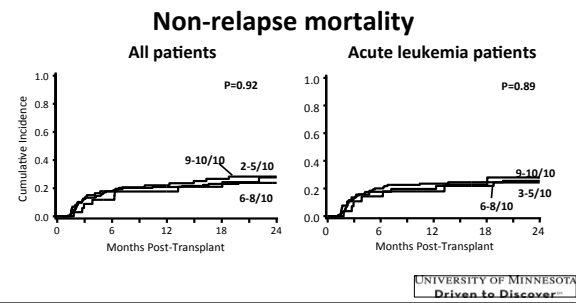


Eapen et al. Blood 2014

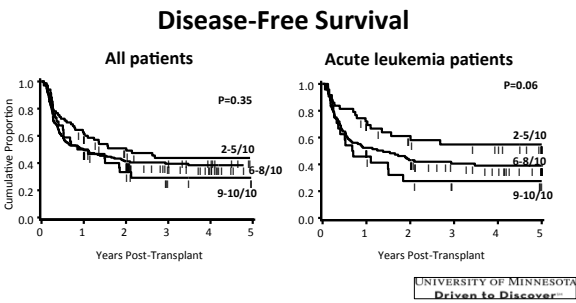
Effect of High Resolution HLA Matching on Outcomes of Double UCB Transplantation



Effect of High Resolution HLA Matching on Outcomes of Double UCB Transplantation



Effect of High Resolution HLA Matching on Outcomes of Double UCB Transplantation



Treatment Failure – Acute Leukemia

HLA-match long-term engrafting unit

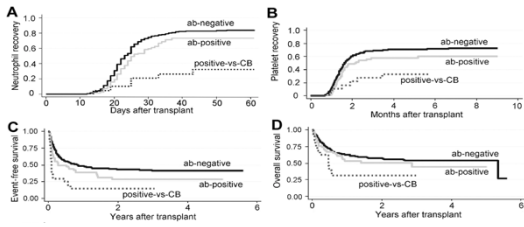
2-5/10	1.0	
6-8/10	1.4 (0.8-2.4)	.20
9-10/10	2.1 (1.1-4.2)	.03

Leukemia Status and Cytogenetics

CR1 non-poor risk cytogenetics	1.0	
CR1 poor risk cytogenetics	0.8 (0.5-1.5)	.57
CR2 with CR1 ≤ 1 year	1.1 (0.6-2.2)	.74
CR2 with CR1 > 1 year	0.8 (0.4-1.6)	.56
CR3	2.3 (1.0-5.2)	.06
Not in remission	3.2 (1.4-7.3)	<.01

UNIVERSITY OF MINNESOTA
Driven to Discover™

Should donor specific anti-HLA antibodies be considered in the selection of cord blood units?



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Takanashi M et al. Blood 2010;116:2839-2846

Adverse Impact of Donor Specific Anti-HLA Antibodies on Double UCBT is Less Clear

	MN Brunstein BMT 2011	Boston Cutler Blood 2011	
MFI	>500	>1000	
No DSA	108	55	
DSA 1 unit	12	11	
DSA 2 units	6	7	
Graft failure	14%	5.5%	
DSA 1 unit	25%(3 of 12)	18% (2 of 11)	
DSA 2 units	16% (1 of 6)	57% (3 of 7)	
Irrelevant Aby	16%	NA	
MFI	>1000	>1000	>1000
DSA 1 unit	40% (2 of 5)	18% (2 of 11)	4 of 16 (25%)
DSA 2 units	25% (1 of 4)	57% (3 of 7)	4 of 11 (36%)

Cord Blood Selection

Cryopreserved nucleated cell dose 2.5-3.0 x 10e7/kg

HLA DRB1 at allele level
HLA A and B at antigen level

Tie Breakers

- CD34 cell dose
- High resolution HLA matching
- Matching at HLA-C
- Direction of mismatch
- Mismatching Kir-ligand
- Non-inherited maternal allele
- Anti-HLA antibodies
- Experience with the cord blood bank
- Red cell depleted
- Licensed vs unlicensed cord blood

Practical Example

- High resolution HLA-matching could be considered in patients with multiple suitable 5/6 and 6/6 HLA-matched unit available

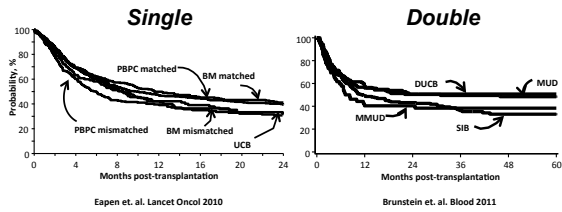
Cryopreserved TNC x10e7	Conventional HLA-match	High res HLA-match
3.5	6/6	5/6
4.5	5/6	5/6
5.5	5/6	3/6

Practical Example

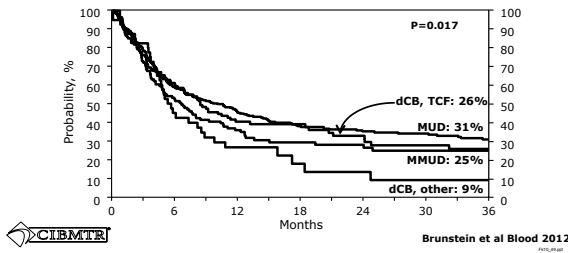
- Similar concept may apply to HLA-C matching

Cryopreserved TNC x10e7	Conventional 6-loci HLA-match	Conventional 6-loci + HLA-C match
3.5	6/6	Mismatch or 6/8
4.5	5/6	Match or 7/8
5.5	5/6	Mismatch or 5/8

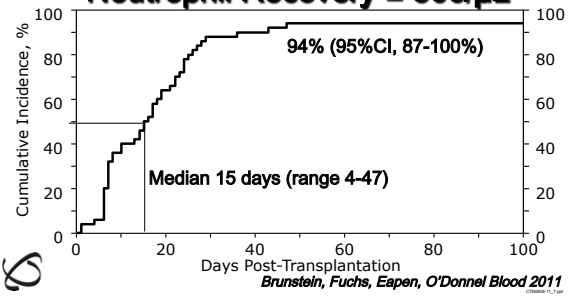
Overall, patients who have a suitably dose single unit or double unit cord blood grafts have outcomes similar to recipients of unrelated donor grafts

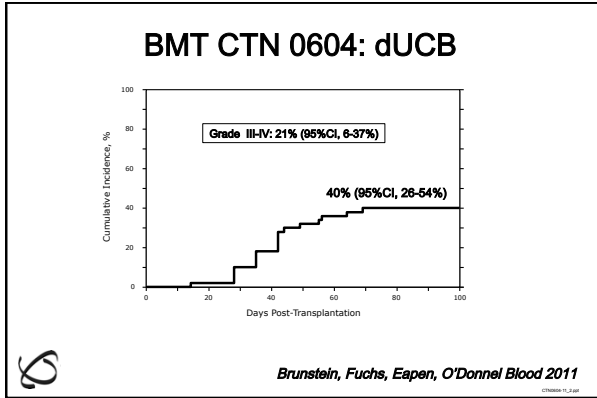


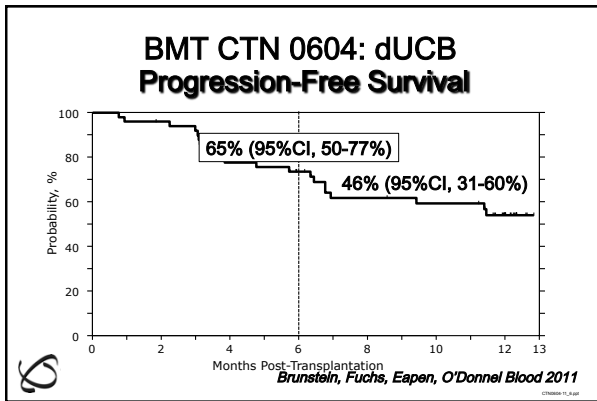
**Leukemia-Free Survival after URD vs double UCB
Reduced Intensity Transplantation for Acute Leukemia**

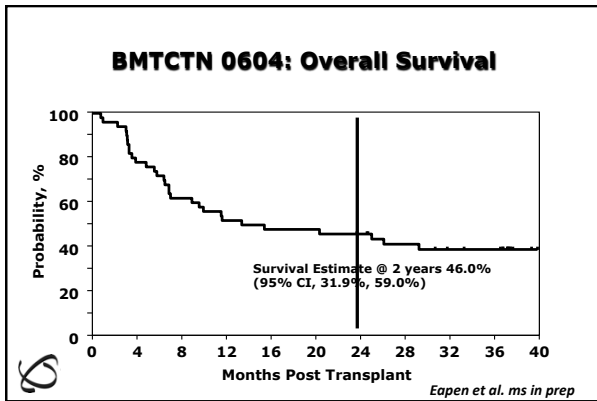


**BMT CTN 0604: dUCB
Neutrophil Recovery $\geq 500/\mu\text{L}$**

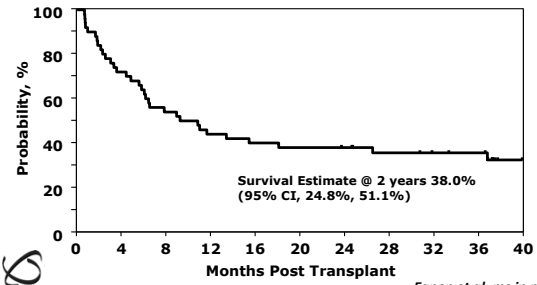




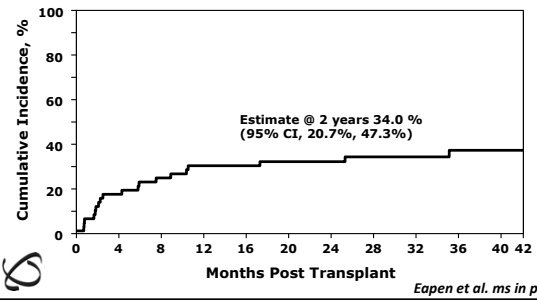




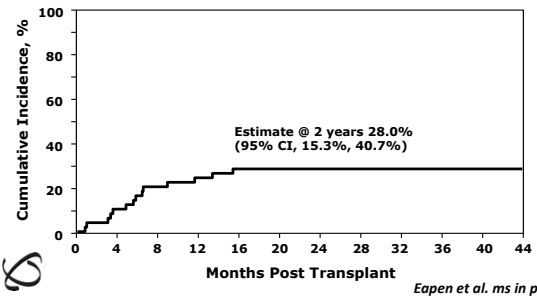
BMTCTN 0604: Progression-free Survival

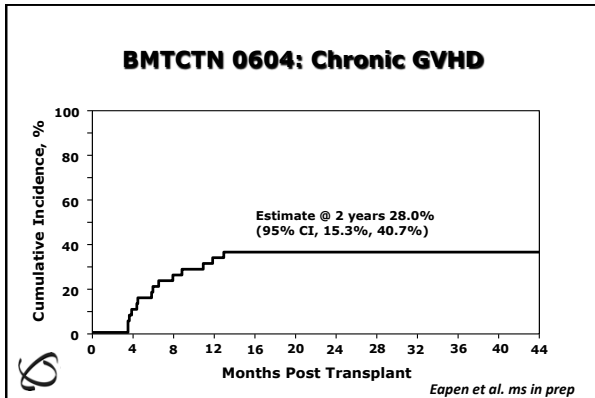


BMTCTN 0604: Relapse



BMTCTN 0604: Treatment Related Mortality





In summary

- UCB is a efficacious source of HSC for the treatment of children (more frequently single) and adults (more frequently double).
- Retrospective comparative data suggests outcomes similar to adult donor types.
- Improved graft selection and novel strategies may further improved UCBT outcomes.
- Ongoing and future prospective studies with help further define the role of UCB in HSC transplantation

What are the two main criteria for the selection of UCB units?

- Viability and nucleated cell dose
- Matching at HLA C and date of cryopreservation
- NIMA and blood type
- HLA matching at A, B and DRB1 and cell dose
- KIR-matching and anti-HLA antibodies

CSBCTR
JMBST

The INCORRECT statement is:

- a. Data suggest that DFS after UCB transplantation is similar to that of adult donor grafts
- b. Single and double UCB grafts are more frequently used for children and adults, respectively
- c. HLA-C may be used to refine UCB unit selection
- d. HLA antibodies are irrelevant in UCB selection
- e. Ongoing clinical trial is randomizing double UCB vs. Haplo donors

SBMT
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