Recent advances of cord blood transplantation in Japan

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COI disclosure

There is nothing to disclose.
Distribution of each donor source in Japan

(Kawakita T, Rinshoketsueki, 2013)

CBT ≈ UBM(PB) ≈ Related BM/PB
Cumulative no. of CBT in Japan surpassed 10,000
(Press release 2013/9/2)

Cumulative no. of CBT up to 2014: 11,587
≈ 1/3 of total CBT performed in the world
### UCB vs. UBM Meta-analysis

<table>
<thead>
<tr>
<th>Study ID</th>
<th>UCB (HR, 95% CI)</th>
<th>UBM</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children subgroup</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jacobsohn 2004</td>
<td>1.91 (0.95, 3.84)</td>
<td>2.93</td>
<td></td>
</tr>
<tr>
<td>Rocha 2001</td>
<td>1.53 (1.21, 1.92)</td>
<td>26.85</td>
<td></td>
</tr>
<tr>
<td>Subtotal</td>
<td>1.56 (1.26, 1.95)</td>
<td>29.78</td>
<td></td>
</tr>
<tr>
<td>adults subgroup</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Altura 1 2009</td>
<td>1.37 (1.07, 1.75)</td>
<td>23.85</td>
<td></td>
</tr>
<tr>
<td>Altura 2 2009</td>
<td>1.07 (0.78, 1.46)</td>
<td>14.56</td>
<td></td>
</tr>
<tr>
<td>Rocha 2004</td>
<td>1.18 (0.95, 1.46)</td>
<td>32.01</td>
<td></td>
</tr>
<tr>
<td>Subtotal (I² = 0.0%, p = 0.445)</td>
<td>1.22 (1.05, 1.40)</td>
<td>70.22</td>
<td></td>
</tr>
<tr>
<td>Overall (I² = 27.8%, p = 0.238)</td>
<td>1.31 (1.16, 1.48)</td>
<td>100.00</td>
<td></td>
</tr>
</tbody>
</table>

- **Engraftment**: better
- **TRM**: better
- **a/c GVHD**: better
- **Relapse**: ≈
- **LFS**: better
- **OS**: better

(Zhang, et al. BBMT, 2012)
Donor selection algorithm for standard risk disease in Japan

Allo-SCT candidate

HLA matched related donor available?

Yes

1MMRD  UCB  1MMUD

Transplant from MRD

No

MUD

Haploidentical donor
(Under investigation)
Major obstacles in CBT

• Engraftment failure

• Relapse
Two types of WBC kinetics in those who had engraftment failure

Primary engraftment failure
n=35

Group 1
n=10
WBC count continuously below 100/μL

Group 2
n=25
WBC count transiently increased above 100/μL

35/μL (30-100) (WBC count medium)

320/μL (130-2900)

(Ota et al. ASH 2011)
Chimeric status in each group

Group 1

- Whole PB/BM
  - Day 14
  - Day 28
- T-cell

Group 2

- Whole PB/BM
  - Day 14
  - Day 28
- T-cell

Graft rejection

Poor graft function

- ● donor type ≥ 50%
- ○ donor type < 50%

(Ota et al. ASH 2011)
TNC and neutrophil recovery

- Higher TNC count → higher and faster neutrophil engraftment

• Presence of anti-HLA antibodies against donor CB (donor-specific antibodies, DSA) was associated with lower incidences of neutrophil recovery.
Are there any impact of anti-HLA antibodies against HLA loci not typed before transplant?

(Anti-HLA antibodies)

B57 B42 B73 B55 B7 B27 B54 B39 B56 B38 B41 B45 B59 B76 B44 B37 Cw7 DP1 DP3 DQ4 DQ8
Possible implication of unrecognized anti-HLA antibodies on engraftment failure

All patients (n=175)
HLA 0-2 / 6 mismatched CBT

Group A vs B  
\[ P=0.13 \]

HLA 2 / 6 mismatched CBT  
(n=123)

Group A  : 90%  
(n=40)
Ab-negative  : 83%  
(n=106)
Group B  : 65.5%  
(n=29)

Group A vs B  
\[ P=0.03 \]

(Hamamoto H, et al. BBMT;2014)
Two types of WBC kinetics in those who had engraftment failure

Primary engraftment failure
n=35

Group 1
n=10
WBC count continuously below 100/µL

Group 2
n=25
WBC count transiently increased above 100/µL

(Ota et al. ASH 2011)
Typical clinical course of Group 2 patient.
(40y, Female, Follicular Lymphoma)

RI-CBT

% Donor cells in BM and T cells

98.8% 100% 96.8%

Severe pre-engraftment immune reactions (Severe PIR)

Hemophagocytic syndrome (HPS)

WBC (×10⁹/l)
Lymph (×10⁹/l)

LDH (U/L)
AST (U/L)

BT (℃)

(Yamamoto et al. AJH 2009)
Antecedent severe PIR has significant impact on development of HPS

PIR (yes or no)

HR 1.78 (0.86-3.68) \( P= 0.11 \)

Severe PIR (yes or no)

HR 14.72 (7.31-19.61) \( P< 0.01 \)

(Yamamoto et al. APBMT 2013)
Mechanism of HPS development

**MMF**

For elderly patients
Since 2005

Donor CTLs

Activated Donor CTL

inflammatory cytokines

IFNγ, TNFα, M-CSF, IL-6, ...

CD47 down regulation

(Kuriyama et al. Blood 2012)

Disruption of don’t eat me signal

MMF

Donor HLA

Mismatched HLA

Host HLA

Phagocytosis

Disruption of don’t eat me signal

SIRPα

HSC

CD47 ↓↓
More intensive GVHD prophylaxis using MMF reduced early NRM and improved incidence of neutrophil recovery

(Uchida N, et al. Transplantation 2011)
More intensive GVHD prophylaxis reduced NRM and improved OS in aged patients

Patients ≥60 y.o. who received Tac+MMF as GVHD prophylaxis showed decreased NRM and better OS after CBT

(Uchida, et al. EBMT 2011)
Incidence of neutrophil recovery has been improving in recent years.

Recent (2011-2013): 86.8%
Middle (2007-2010): 77.3%
Early (2003-2006): 70.7%

P < 0.01

(Yamamoto H, et al. unpublished data)
Major obstacles in CBT

• Engraftment failure

• Relapse
More relapse rate in CBT? → No!

<table>
<thead>
<tr>
<th>Group</th>
<th>Donor type</th>
<th>No. HLA mismatch</th>
<th>Diagnosis</th>
<th>Relapse</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eurocord-EBMT</td>
<td>CB</td>
<td>0</td>
<td>Various including non-malignancy</td>
<td>48% of death</td>
<td>New Engl J Med 2000</td>
</tr>
<tr>
<td>Related BM</td>
<td></td>
<td>0</td>
<td></td>
<td>49% of death</td>
<td></td>
</tr>
<tr>
<td>IBMTR &amp; NCBP</td>
<td>CB</td>
<td>1~2</td>
<td>AML, ALL, CML, MDS</td>
<td>26/150 (17%)</td>
<td>New Engl J Med 2004</td>
</tr>
<tr>
<td>Unrelated BM</td>
<td></td>
<td>0</td>
<td>AML, ALL, CML, MDS</td>
<td>83/367 (23%)</td>
<td></td>
</tr>
<tr>
<td>Unrelated BM</td>
<td></td>
<td>1</td>
<td>AML, ALL, CML, MDS</td>
<td>12/83 (14%)</td>
<td></td>
</tr>
<tr>
<td>Eurocord &amp; EBMT</td>
<td>CB</td>
<td>0~3</td>
<td>AML, ALL</td>
<td>23%</td>
<td>New Engl J Med 2004</td>
</tr>
<tr>
<td>Unrelated BM</td>
<td></td>
<td>0</td>
<td>AML, ALL</td>
<td>23%</td>
<td></td>
</tr>
<tr>
<td>JCBBN &amp; JMDP</td>
<td>CB</td>
<td>0~2</td>
<td>AML</td>
<td>31% (2yr)</td>
<td>Blood 2009</td>
</tr>
<tr>
<td>Unrelated BM</td>
<td></td>
<td>0</td>
<td>AML</td>
<td>24% (2yr)</td>
<td></td>
</tr>
<tr>
<td>Related PB</td>
<td></td>
<td>0</td>
<td>AML</td>
<td>24% (2yr)</td>
<td></td>
</tr>
<tr>
<td>Unrelated BM</td>
<td></td>
<td>1</td>
<td>AML</td>
<td>31% (2yr)</td>
<td></td>
</tr>
<tr>
<td>Unrelated PB</td>
<td></td>
<td>0</td>
<td>AML</td>
<td>24% (2yr)</td>
<td></td>
</tr>
<tr>
<td>CIBMTR &amp; NCBP &amp; EBMT</td>
<td>CB</td>
<td>0~2</td>
<td>AML, ALL</td>
<td>43/165 (25%)</td>
<td>Lancet Oncol 2010</td>
</tr>
<tr>
<td>Unrelated BM</td>
<td></td>
<td>0</td>
<td>AML, ALL</td>
<td>112/332 (34%)</td>
<td></td>
</tr>
<tr>
<td>Unrelated PB</td>
<td></td>
<td>0</td>
<td>AML, ALL</td>
<td>209/632 (33%)</td>
<td></td>
</tr>
<tr>
<td>Unrelated BM</td>
<td></td>
<td>1</td>
<td>AML, ALL</td>
<td>42/140 (30%)</td>
<td></td>
</tr>
<tr>
<td>Unrelated PB</td>
<td></td>
<td>1</td>
<td>AML, ALL</td>
<td>77/256 (30%)</td>
<td></td>
</tr>
<tr>
<td>JCBBN &amp; JSHCT</td>
<td>CB</td>
<td>0~2</td>
<td>AML, ALL, CML, MDS</td>
<td>35% (3yr)</td>
<td>Leukemia 2012</td>
</tr>
<tr>
<td>Related PB/BM</td>
<td></td>
<td>1</td>
<td>AML, ALL, CML, MDS</td>
<td>32% (3yr)</td>
<td></td>
</tr>
<tr>
<td>JCBBN &amp; JMDP</td>
<td>CB</td>
<td>0~2</td>
<td>AML, ALL, MDS</td>
<td>RR=1.28 (95%CI: 0.93-1.76)</td>
<td>Biol Blood Marrow Transplant 2012</td>
</tr>
<tr>
<td>1 (class I)</td>
<td></td>
<td></td>
<td>AML, ALL, MDS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unrelated BM</td>
<td></td>
<td>2</td>
<td>AML, ALL, MDS</td>
<td>RR=1.00</td>
<td></td>
</tr>
</tbody>
</table>
Interval between transplant and relapse in those who have received 2nd transplant using CB

In 15 / 26 patients, remission duration was even longer after CBT compared to their 1st transplant using rPB/uBM

(Yamamoto H, et al. unpublished data)
Disease relapse is dependent on intensity of pre-transplant conditioning

>60yr MDS/secondary AML

Relapse: MAC \(<\) RIC \((P<.01)\)
NRM: MAC \(>\) RIC \((P=.03)\)
OS: MAC \(\approx\) RIC \((P=.51)\)

(Lim Z et al. JCO 2010;28:405-411)
Consistent AUC is achieved by ivBu than oral Bu

Busulfan plasma exposure (AUC in µM.min)

Target AUC

I.V. busulfan

Oral busulfan

Relapse ↑

Graft failure ↑

VOD ↑
Prospective multicenter study: JSCT FB09

Flu/ivBu4

Patients: 55-70 y.o. AML, MDS
No. enrolled: 38

Day

-7  -6  -5  -4  -3  -2  -1  0

Iv Busulfan

Fludarabine

TBI 4Gy

Allo-SCT
Flu/ivBu4 is feasible for elderly

(Takama H, et al. Bone Marrow Transplant 37;345-351, 2006)

(Uchida, et al. Submitted)

<54 yo

55—70 yo

Comparable PK

Low NRM at day 60 post-transplant was observed.

(Uchida N. et al. JSCT. submitted)
Flu/ivBu4 showed better OS, irrespective of donor type

Overall survival

(95% CI)
1Y 0.632 (0.459-0.763)
2Y 0.579 (0.408-0.717)

(95% CI)
1Y,2Y 0.625 (0.229-0.861)
1Y 0.688(0.405-0.856)
2Y 0.562(0.295-0.762)

(Uchida N. et al. JSCT. submitted)
Relapse incidence is still high after Flu/ivBu4

Cumulative incidence of relapse

All cases

Sub group

(95% CI)
1Y 0.245 (0.082-0.380)
2Y 0.311 (0.130-0.455)

1: Matched RD
1Y 0.375 (0.072-0.694)
2Y 0.339 (0.093-0.611)

2: Mismatched RD/UBD
1Y 0.245 (0.053-0.509)
2Y 0.339 (0.093-0.611)

3: CBD
1Y 0.148 (0.020-0.391)
2Y 0.233 (0.049-0.494)

Years post-transplant

CB

MRD

MMRD / UBM

(Uchida N. et al. JSCT. submitted)
Another non-TBI conditioning: Flu / Bu4 / Mel80 Regimen

Day: -7 -6 -5 -4 -3 -2 -1 0

- Flu: 30 mg/m²/day
- iv Bu: 3.2 mg/kg/day
- Mel: 40 mg/m²

Tacrolimus (Tac) ± MMF

(Yamamoto H, et al. ASH 2013)
Possible advantage of Flu/ivBu4/Mel80 Regimen

- Adding Mel to Flu/Bu4 → Increase antitumor effect
  Double alkylating agents
- Melphalan has immunosuppressive effect  
  → Reliable Engraftment
- A toxic profile does not overlap  
  → Decrease NRM

Properties | BU | Cy | Mel |
--- | --- | --- | --- |
Immunosuppression | - | ++ | ++ |
Liver toxicity & VOD | +++ | +++ | - |
Pneumonitis | ++ | + | - |
CNS toxicity | +++ | - | - |
Mucositis | ++ | - | +++ |
Cardiotoxicity | - | ++ | - |
BM suppression | +++ | + | +++ |
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n</td>
<td>51</td>
</tr>
<tr>
<td>Median Age, (range)</td>
<td>59 (19-70)</td>
</tr>
<tr>
<td>Disease</td>
<td></td>
</tr>
<tr>
<td>AML</td>
<td>43 (84.3%)</td>
</tr>
<tr>
<td>MDS (RAEB-II)</td>
<td>3 (5.8%)</td>
</tr>
<tr>
<td>CML (BC)</td>
<td>5 (9.8%)</td>
</tr>
<tr>
<td>Disease status</td>
<td></td>
</tr>
<tr>
<td>Untreated / Blast control</td>
<td>14 (27.4%)</td>
</tr>
<tr>
<td>Primary induction failure</td>
<td>17 (33.3%)</td>
</tr>
<tr>
<td>Relapse 1</td>
<td>12 (23.5%)</td>
</tr>
<tr>
<td>Relapse ≥2</td>
<td>8 (15.6%)</td>
</tr>
<tr>
<td>Non remission</td>
<td>51 (100%)</td>
</tr>
</tbody>
</table>

(Yamamoto H, et al. ASH 2013)
Sufficient engraftment rate was observed

Cumulative incidence of Engraftment: 90.2%

Median: 19.5 days (range, 13-38)

Cumulative incidence

Achievement: 46 / 51
Early relapse: 3
NRM: 2
Rejection: 0
HPS: 0

Days after transplant
(Yamamoto H, et al. ASH 2013)
Flu/ivBu4/Mel80 showed remarkable OS and PFS

Median follow up of survivor: 851 (391-2386) days post-transplant

2y OS: 56.5%
2y DFS: 56.5%

(Yamamoto H, et al. ASH 2013)
Flu/ivBu4/Mel80 regimen showed sufficient anti-tumor activity without increasing NRM

Median follow up of survivor: 851 (391-2386) days post-transplant

Cumulative incidence of relapse

REL at 2 year: 20.0%

Cumulative incidence of NRM

NRM at 2 year: 23.9%

(Yamamoto H, et al. ASH 2013)
## UBM vs. CB

(recent Japanese registry data)

N=3,062 (Japanese registry (TRUMP) data)
16-50 y.o.
Transplanted between 2001-2010

<table>
<thead>
<tr>
<th>Disease</th>
<th>Donor type</th>
<th>N</th>
<th>HR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>AML</td>
<td>8/8 UBM</td>
<td>676</td>
<td>Ref.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>7/8 UBM</td>
<td>455</td>
<td>1.27</td>
<td>1.06-1.52</td>
<td>0.009</td>
</tr>
<tr>
<td></td>
<td>6/8 UBM</td>
<td>204</td>
<td>1.33</td>
<td>1.06-1.67</td>
<td>0.015</td>
</tr>
<tr>
<td></td>
<td>UCB</td>
<td>617</td>
<td>1.08</td>
<td>0.91-1.29</td>
<td>0.37</td>
</tr>
<tr>
<td>ALL</td>
<td>8/8 UBM</td>
<td>418</td>
<td>Ref.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>7/8 UBM</td>
<td>267</td>
<td></td>
<td>n.s.</td>
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<tr>
<td></td>
<td>6/8 UBM</td>
<td>120</td>
<td></td>
<td>n.s.</td>
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</tr>
<tr>
<td></td>
<td>UCB</td>
<td>305</td>
<td></td>
<td>n.s.</td>
<td></td>
</tr>
</tbody>
</table>
Conclusion

• No. of CBT in Japan has been increasing. More than 11,000 CBT has been done, which accounts for 1/3 of total number of CBT performed in the world.

• Mechanisms behind graft failure have become clearer than before, which results in decrease of engraftment failure. The rate of engraftment has now become almost comparable to that following UBMT.

• Immune cells of CB can be very active from early time point post transplant. Attempt to intensify pretransplant conditionings using ivBu showed better survival by reducing relapse without increasing NRM.
Donor selection algorithm for standard risk disease in Japan

Allo-SCT candidate

HLA matched related donor available?

Yes

Transplant from MRD

1MMRD  UCB  1MMUD

No

= MUD

Haploidentical donor
(Under investigation)
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JSCT FB09 Participating institutes

Sapporo Medical University Hospital First Department of Internal Medicine
Sapporo Medical University Hospital Fourth Department of Internal Medicine
Asahikawa Medical College Hospital Third Department of Internal Medicine
Iwate Medical University School of Medicine Hematology/Oncology, Department of Internal Medicine
Akita University School of Medicine Division of Hematology and Oncology, Department of Medicine
Fukushima Medical University Hospital Department of Hematology
Kita-Fukushima Medical Center Hematology
Saiseikai Maebashi Hospital Leukemia Research Center
Kameda General Hospital Division of Hematology/Oncology, Department of Medicine
National Cancer Center Hospital Hematopoietic Stem Cell Transplantation Division
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Gifu Municipal Hospital Department of Hematology
Toyota Memorial Hospital Department of Hematology
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Kurume University School of Medicine Division of Hematology, Department of Medicine
National Kyushu Cancer Center Department of Hematology
National Hospital Organization Kyusyu Medical Center Department of Hematology
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(APBMT 2011 in Sydney)
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Abe M.

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Kageyama K.

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Dept.Pharmacy
Saegusa & staffs

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Toranomon Hospital

Dept.Infect Dis

Dept.Physical Ther

Dept.Med

Dept.Pharmacy

Dept.Med

Dept.Transfusion Med