Efforts to Increase Cord Blood Utilization

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Acknowledgements
MSKCC Staff, NMDP, NYBC, HRSA. Colleagues at the U of Minnesota & many other national & international centers & CB banks.

Disclosures
Unrestricted educational graft funding: Gamida Cell & Merck. Clinical trial funding: Angiocrine Bioscience.
Major Benefits of CBT

1) Extending transplant access:
   • Rapid availability & easy scheduling.
   • Many patients have good units.
   • Reduced requirement for HLA-match.
   • For some, CB is only available stem cell source.

2) Long-term advantages:
   • Good immune recovery.
   • Better GVHD treatment responses.
   • Low rates chronic GVHD.
   • Low relapse rates (no ATG).
   • Advantages in GVL biology.
   • Long-term cost benefits.

Supported by single center/ multi-center (eg U of MN, FHCRC, MSKCC, Duke, Colorado, Great Ormond St, Duke, Utrecht, Milan) & registry studies.
Major Benefits of CBT

**However, not all of the transplant community ree.**

**Vastly opposing opinions re the value of CB.**

Supported by single center/ multi-center (eg U of MN, FHCRC, MSKCC, Duke, Colorado, Great Ormond St, Duke, Utrecht, Milan) & registry studies.
Utilization of CB has Declined: Reasons

- **Unit selection**: more complicated than URD/ haplo.
- **Cost** of units/ longer early hospital stay.
- **Complexity**: early post-transplant.
- **Selective focus**: reduced relapse & cGVHD ignored.
- CBT as “last ditch” therapy.
- **Expansion**: adverse effect on CBT without expansion?
Transplant Access

**Q:** Do you need CB?  **A:** Yes

**Why?**

**Q:** Is there ongoing disparity in unrelated donor (URD) access according to patient race?  **A:** Yes.
Likelihood of Undergoing an 8/8 URD Transplant According to Patient Ancestry by Era (n = 1,312)

Major problems with adult volunteer donor access: not appreciably improving for southern & non-European patients.

Barker et al, Blood Advances 2019
U.S. Population Becoming More Diverse

Young patients URD match rate getting worse:
• Patient > 60 yrs: 54%
• Patient < 20 yrs: 34%.

Young donors less likely to match patients of any age:
• 48% of new donors aged < 35 yrs have unique HLA.
• 60% if Asian/ Hispanic.
• 78% if Black.

Thus, not going to get better.
This makes the CB inventory very important.

Data courtesy of NMDP Be the Match, 2018
Haplo graft availability by patient ancestry if no 8/8 URD (n = 81 patients evaluated)

<table>
<thead>
<tr>
<th>Ancestry</th>
<th>N (%) of Group with Suitable Haplo Graft</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>European (n = 37, 46%)</td>
<td>31/37 (84%)</td>
<td>0.008</td>
</tr>
<tr>
<td>African (n = 16, 20%)</td>
<td>7/16 (44%)</td>
<td></td>
</tr>
<tr>
<td>Other Non-European (n = 28, 34%)</td>
<td>23/28 (82%)</td>
<td></td>
</tr>
</tbody>
</table>

- Racial differences in access to haplo-identical donors.
- Other limitations: delays with donor clearance or if must workup multiple donors or if use extended family.

* donors targeted by recipient DSA allowed.  

Kosuri et al, BBMT 2017
MSK CBT by Patient Ancestry 2005 - 2017 (n = 301)

Europeans: blues.
Non-Europeans: red-yellow-brown

Reduced requirement for HLA-match (median HLA-match in adult CBTs 5/8)
CB extends transplant access to all

Barker et al, Blood Advances 2019
TNC & CD34+ Cell Dose Distribution in NMDP U.S. Inventory for a 70 kg Patients (n = 126,000 Units)

1) Majority of units with adequate TNC do not have adequate CD34+ dose.
2) 4% adequate as single units.
3) With lower dose (TNC 1.5 & CD34+ 1.0) threshold, 22% of units had adequate dose for a double unit graft.

Barker et al, Blood Advances 2019

This data supports major focus should be on increasing inventory of high dose units ie increase lower limit of TNC for banking.
MSK: CB Graft Availability if No 8/8 URD (n = 164)
(adults, nearly all doubles, units 4-6/6 & ≥ 3/8 HLA-matched)

- Despite small inventory, adequate CB graft: 88%.
- Many have excellent grafts.
- Graft availability much better than URD eg more than triple for African ancestry pts.
- No CB graft: 12%.

(nearly all non-European, median weight 98 kg).

Barker et al, 2019 (manuscript submitted)
“Nearly everyone has a CB graft & you don’t have to worry about donor availability”
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“Yes – but engraftment is slow & early TRM is high”

and

“You can only do CBT with expansion*”

*Limitations of expansion: logistics, more complicated, possible compromise of T-cells with T-add back platforms?
Can we make CBT easier?
Strategies to Reduce Mortality *without* Expansion

1st) Efficient URD/ CB searches (& haplo workups).

2nd) Unit selection:
   - Quality, CD34+ dose & 8 allele HLA-match.
   - Double unit grafts if needed.

3rd) Conditioning

4th) Day 0 optimal thaw & post-thaw quality assessment.

5th) Optimize immune suppression.

6th) Other:
   - Management of slow engraftment.
   - PES: prevention & therapy.
   - aGVHD & CMV: prevention & therapy.
   - other complications.

*Barker et al, BBMT Optimal Practices 2017*
1st) CBT Recipients Benefit from Efficient URD Searches
MSKCC 8/8 URD Search Prognosis using NMDP Haplologic Predictions

No matched Sibling ➔ Evaluate search for 8/8 URD

Very Good/Good: 8/8 URD transplant

Fair: Pursue URDs & alternative donors

Poor/V. Poor/Futile: Abandon 8/8 URD

Alternative Donors

Only need high resolution typing & prelim search

Can predict 8/8 URD likelihood at search initiation

Davis et al, BBMT 2018
MSK Algorithm: Efficient Donor Searches

No Sib

Evaluate search for 8/8 URD

Very Good/Good → 8/8 URD transplant

Fair

Poor/V. Poor/Futile

Alternative Donors

Cord Blood

Haplo

MM URD

Urgent

Promptly permits pursuit of alternative donors if needed.

Davis et al, BBMT 2018
2\textsuperscript{nd} Optimal Unit Selection: Quality, Dose, HLA-match

ASTCT CB SIG & NMDP Unit Selection Guidelines

- **Unit quality**: eg RBC depleted, standard cryoprocessing

- **Cell Dose**:
  - Single unit: TNC $\geq 2.5$ & CD34+ $\geq 1.5$
  - Double unit: TNC $\geq 1.5$ & CD34+ $\geq 1.0$

- Higher doses ideal.

- **8 allele HLA-match** (HLA-A, -B, -C, -DRB1)
  - Guidelines $\geq 4/8$ (MSKCC $\geq 3/8$ to extend access)

Need to make a distinction between adults & pediatrics, & patient diagnosis. How to trade off between dose (TNC/CD34+) & allele HLA-match?: unknown.
3rd) Conditioning: Examples

High*
Cy 120
Flu 75
TBI 1375

Mini**
Cy 50
Flu 150
TBI 200

Midi***:
Cy 50
Flu 150
Thio 10
TBI 400

Tailor intensity to pt age & comorbidity status (“fitness”: aaHCT-CI)

MSKCC Midi Prep for Adults
Cy 50/ Flu 150/ Thio 10/ TBI 400 + dCBT

• Adults ≤ 65 yrs.
• High risk heme malignancies.

Ablative but intermediate intensity

* ATG abandoned in 2005

Ponce et al, BBMT 2013
Politikos et al, TCT 2019 (manuscript in preparation)
4th) Optimize Thaw & Infusion
Rapid analysis of post-thaw CD34+ viability*.
Nursing guidelines for infusion**.

* Scaradavou et al, BBMT 2009
**Dahi et al, BBMT 2014
5th) Importance of Immune Suppression: eg CSA & MMF

Association between N of days sub-therapeutic CSA between days -1- to +7 & day 100 severe aGVHD.

\[ P = 0.021 \]

At least one day (n = 101)

No days (n = 30)

Days from dCBT

C. I. of grade III-IV aGVHD

Sub-therapeutic CSA days -1 - +7: increased risk of severe acute GVHD.

Bhatt et al, TCT 2018

Multivariate Analysis:

is MMF Dose Associated with Day 100 Grade III-IV aGVHD Risk?
(Also included pt age, gender & CMV status).

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMF Dose &amp; Dominant Unit-Recipient HLA-Match</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low Dose &amp; Worse Match (n = 30)</td>
<td>0.23 (0.03-1.84)</td>
<td>0.05</td>
</tr>
<tr>
<td>High Dose &amp; Worse Match (n = 18)</td>
<td>0.46 (0.20-1.07)</td>
<td></td>
</tr>
<tr>
<td>Low Dose &amp; Better Match (n = 71)</td>
<td>0.26 (0.09-0.75)</td>
<td></td>
</tr>
<tr>
<td>High Dose &amp; Better Match (n = 55)</td>
<td>Reference</td>
<td></td>
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</table>

Total daily dose split at median.
Worse HLA-match: 1-3/6 alleles (vs 4-6/6).

Increased MMF dose: offset adverse impact of more HLA-mismatch.

Harnicar et al, BBMT 2015
Q: Can focusing on optimizing multiple components of the transplant improve post-transplant survival?

A: Yes.
MSKCC Adult Midi Prep dCBT (n = 102, 2014-2017)

Median survivor follow-up: 40 months (range 20-67)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
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<tbody>
<tr>
<td>Median Age</td>
<td>50 yrs (range 21-65)</td>
</tr>
<tr>
<td>Median Weight</td>
<td>80 kg (range 36-137)</td>
</tr>
<tr>
<td>N (%) Diagnosis</td>
<td></td>
</tr>
<tr>
<td>Acute leukemia*</td>
<td>71%</td>
</tr>
<tr>
<td>MDS/ CML/ other MPD*</td>
<td>17%</td>
</tr>
<tr>
<td>NHL</td>
<td>14%</td>
</tr>
<tr>
<td>Median HLA-match units to patient</td>
<td>5/8 (range 3-7)</td>
</tr>
<tr>
<td>Median CD34+ cell dose (infused 10^5/kg/unit)</td>
<td>1.3 (range 0.2-8.6)</td>
</tr>
</tbody>
</table>

* Myeloids ≤ 10% & ALL < 5% blasts pre-CBT

Politikos et al, TCT 2019
MSK Midi dCBT (n = 102 adults)

- Adults median 50 yrs (21-65).
- High risk heme malignancies.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Value</th>
</tr>
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<tbody>
<tr>
<td>Day 45 engraftment</td>
<td>97% (Median +25 days)</td>
</tr>
<tr>
<td>Day 180 grade III-IV aGVHD</td>
<td>23% (II-IV: 77%)</td>
</tr>
<tr>
<td>1-yr cGVHD</td>
<td>4%</td>
</tr>
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</table>

Politikos et al, TCT 2019
MSK Midi dCBT: Progression-Free Survival (n = 102)

All patients: 74% @ 2 yrs
MSK Midi dCBT Progression-Free Survival (n = 102) by Patient Co-morbidities

High comorbidity score (aaHCT-CI ≥ 4)
(n = 38; 61% @ 2 yrs)

Low comorbidity score (aaHCT-CI 0-3)
(n = 64; 81% @ 2 yrs)

p = 0.024
MSK Midi dCBT Progression-Free Survival (n = 102) by Patient Disease Risk

- Low or Intermediate Risk (rDRI)
  - (n = 74; 80% @ 2 yrs)

- High or Very High (rDRI)
  - (n = 28; 57% @ 2 yrs)

\[ p = 0.081 \]
MSK Midi dCBT Progression-Free Survival:
Acute Leukemia (n = 70)

Acute leukemias: 76% @ 2 yrs
Patients do recover – including if prior aGVHD.

Median day 120 CD4+ count: 204.

Politikos et al, 2019 (manuscript submitted)
MSKCC: Major Problems in Adult CBT

- Acute GVHD - esp. GI tract.  
  (~20% grade III-IV aGVHD).

- Early CMV infection.  
  (~60% seropositive & > 80% CMV+ will reactivate).
Midi Cy/ Flu/ Thio/ TBI dCBT + Day -1 Tocilizumab (n = 26)

- Adults ≤ 65 yrs.
- High risk heme malignancies.

Unmanipulated: #1.
Unmanipulated: #2.

As per G. Hill group.
Toci 8 mg/kg.

Preliminary data (2018-2019):
- decreased grade 3-4 aGVHD: 4%.
  (1 pt with grade 3, no grade 4).

Updated from Politikos et al, TCT 2019
CMV Infections in Adult CMV+ CBT Recipients with Letermovir Prophylaxis

- Start letermovir day +7.
- Very effective (0%).
- No toxicity.
- Cost effective.
- New standard of care.
- Do not know when can safely stop.

Lau, C. et al, 
manuscript in preparation, 2019
Despite multiple centers & trials showing outstanding results, CBT has declined in U.S. & Europe.

**How to Fix?**

*Note: increased utilization of CB units will help patients & save the banks.*
How to Correct CBT Decline?: Increase Interest/Need/ Ease

BLACK: not working to date.
BLUE: will not be enough.
RED: will help.

Field:
- Emphasize major advantages & good outcomes with CBT (especially in experienced centers).
- Offer advice to MDs who ask.
How to Correct CBT Decline?: Increase Interest/Need/Ease

• Ensure timely **referral** for transplant eligible pts.

• Efficient URD/ CB searches (& haplo workups). Stop futile URD searches.

• CB unit selection: make it much easier. Ensure optimal units selected.

**Field:**
- Emphasize major advantages & good outcomes with CBT (especially in experienced centers).
- Offer advice to MDs who ask.

**BLACK:** not working to date.
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**RED:** will help.

• **Optimal practice guidelines.**
Proposal: Create a U.S. CBT Network

Aim is to facilitate:
• Rapid collaborations & information exchange.
• Create/ share practice guidelines & protocols & share nationally.
• Speed publications.
• Perform clinical trials.
• Train junior MDs/ other transplant staff.

Likely only approach that will effectively reverse decline in CBT.
Further Benefits of CBT Network

• Create momentum & increase perception in the field.
• Increase enthusiasm → recruit & train more staff in CBT.
• Support CBT centers so they do not abandon CBT.
• Rapidly share knowledge with centers not part of Network.
• Support the CB Banks (including staff morale).
• Provide improved mechanism to lobby insurance companies to pay for CB transplants.

Suggest these efforts be promoted by ASTCT & NMDP: to increase CBT visibility & make CBT more mainstream. Initiative is ambitious & will require funding.