Cord Blood Transplantation in the Era of COVID: Challenges and Opportunities

On behalf of the ASTCT CB Special Interest Group

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Dr Filippo Milano, FHCRC, Seattle
Dr John Wagner, U of Minnesota, Minneapolis
New York Perspective

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Director, MSKCC CBT Program
Professor of Medicine, Weill Cornell Medical College
Chair, ASTCT CB Special Interest Group
Benefits of CB as an Alternative Stem Cell Source
1) Rapid availability & logistics of obtaining graft are easy.
2) Extends access to all - especially non-Europeans

MSKCC: Transplant According to Patient Ancestry (n = 1,312)

Important as U.S. population becomes more diverse.

Barker et al, Blood Advances 2019
2) CBT at MSKCC (n = 319)

- African: n = 58, 18%
- Middle Eastern: n = 11, 3%
- Asian: n = 47, 15%
- European Mix: n = 47, 15%
- Southern European: n = 45, 14%
- Eastern European: n = 32, 10%
- Northwest European: n = 23, 7%
- Non-European Mix: n = 24, 8%

Major extension of access to minorities

Barker et al, Blood Advances 2019
3) Multiple series demonstrate high disease-free survival after CBT for hematologic malignancies: attributed to potent graft-vs-leukemia effects

Example: Adult Double Unit CBT at MSKCC (n = 90)
2014-2017, median 47 yrs (range 21-63), 68% acute leukemia
Intermediate intensity conditioning, median 5/8 HLA-match

**DFS:** 76% (95% CI: 68-86)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Value</th>
</tr>
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<tbody>
<tr>
<td>3-yr transplant-related mortality</td>
<td>15% (95% CI: 8-23)</td>
</tr>
<tr>
<td>3-yr relapse</td>
<td>9% (95% CI: 4-16)</td>
</tr>
<tr>
<td>3-yr overall survival</td>
<td>82% (95% CI: 74-90)</td>
</tr>
</tbody>
</table>

*Barker et al, MSKCC 2020 (unpublished)*
3) Multiple series demonstrate high disease-free survival after CBT for hematologic malignancies: attributed to potent graft-vs-leukemia effects.

These outcomes rival those of any adult donor stem cell source.

<table>
<thead>
<tr>
<th>Months from dCBT</th>
<th>Disease-Free Survival (%)</th>
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<tr>
<td>3-yr relapse</td>
<td>9% (95% CI: 4-16)</td>
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<td>3-yr overall survival</td>
<td>82% (95% CI: 74-90)</td>
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Barker et al, MSKCC 2020 (unpublished)
The Challenge: Decline in CBT

Despite advantages CBT has decreased.

Contributors: complexity of unit selection & early post-CBT care.
Q: If the field has turned to haplo transplants, why continue with CBT?
A: Not all patients have haplo donors.

- **Limitations** if donor is not medically fit or has socio-economic restrictions.
- **Delays** if must work-up multiple donors.
- **Limitations** if pediatric & older donors OR if patient has donor-specific HLA antibodies (frequently women with multiple pregnancies).

At MSKCC, minority of African patients have suitable haplos *Kosuri et al, BBMT 2017.*
Compelling argument in favor of continuing CB banking & CB transplants.

**Problem:** contraction in CBT activity.
CBT Activity in U.S. Transplant Centers
Centers: n = 151

<table>
<thead>
<tr>
<th>N of CBTs/Year</th>
<th>N (%) of TCs</th>
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<tbody>
<tr>
<td>&gt; 5</td>
<td>31/ 151 (21%)</td>
</tr>
<tr>
<td>1-5</td>
<td>46/ 151 (30%)</td>
</tr>
<tr>
<td>0</td>
<td>74/ 151 (49%)</td>
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</table>

Nearly 80% of TCs have little or no CBT experience

Expertise in performing CBT is progressively deteriorating.

Data courtesy of NMDP Be the Match, 2019
ASTCT CB Transplant Guideline Initiative

Led by Drs Filippo Milano & Juliet Barker

- Peds: Malignants
  - Cary Martinez

- Peds: Non-Malignants
  - Priti Tewari

- Patient Selection & Conditioning
  - Leland Metheny

- Unit Selection
  - Ioannis Politikos

- Thaw & Infusion
  - Machi Scaradavou

- Infectious Disease
  - Amanda Olson

- IS & GVHD
  - Doris Ponce

- Engraftment & PES
  - Omar Aljitawi
Covid-19
Result: Rapid deterioration in ability to obtain adult donor grafts (unrelated & sometimes related donors)

- Increase in donors being unavailable.
- No bone marrow collections (ORs are shut).
- Staffing limitations in pheresis suites.
- Donor willing but flight restrictions.
- Need for collection & cryopreservation at TC prior to conditioning adds logistical problems & potential treatment delays.

Prediction: need for CBT will increase.
CBT increase has not happened: why?

Center type

- Center never does CBT- would not consider starting.
- Would consider but lacks expertise.
- Could do CBT but risk of CBT during a pandemic worse than risk of no transplant. *AND* Needed resources not available or uncertain or rationed.
- All transplants cancelled regardless of stem cell source.

Did URD or haplo transplant or transplant delayed or non-transplant therapy: This indicates a major problem with CBT.

CBTs go on hold.
Why is this a problem?

COVID19 could enhance CBT being abandoned.

Will result in denial of CBT therapy to:
- Patients who would have excellent CBT outcomes.
- Patients without other options.

This will exaggerate health care disparities.

HRSA-funded high quality CBUs remain unused
The Opportunity: Re-imagine CBT

Efforts to make CBT a widespread treatment option have failed.

Use COVID disruption to envision & plan dramatic improvements in CB banking & CBT for use in post-pandemic world.

Propose demonstration project to optimize the conduct of CBT in the U.S.
Demonstration Project: Optimize CBT

Collaborate with NMDP to implement simplified unit selection guidelines.

Transplant centers will:
- create unified SOPs for unit selection & CBT activity.
- develop comprehensive CBT-focused professional development modules for coordinators, MDs, nurses, pharmDs, lab staff.
- create & refine common CBT protocols.

Implementation

Transplant centers perform CBT with focus on enhancing survival in minorities & pts with high risk disease.

Collaborate with CIBMTR to analyze transplant outcomes.

Share all via ASTCT.
Fred Hutchinson Cancer Research Center

Seattle Perspective

Why We Should Keep Doing Cord Blood Transplants?

Filippo Milano, MD, PhD
Director Cord Blood Program
Fred Hutchinson Cancer Research Center
University of Washington, School of Medicine
Why we should keep doing cord blood transplants

➢ Outstanding clinical outcomes-especially in high risk disease.
<table>
<thead>
<tr>
<th></th>
<th>CBT (n=140)</th>
<th>MURD (n=344)</th>
<th>MMURD (n=98)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years, (range)</td>
<td>29 (0.6-64)</td>
<td>40 (1-67)</td>
<td>45 (2-64)</td>
</tr>
<tr>
<td>Gender, Female, n (%)</td>
<td>68 (48)</td>
<td>150 (43)</td>
<td>45 (46)</td>
</tr>
<tr>
<td>Weight in kg, (range)</td>
<td>70 (9-112)</td>
<td>76 (13-173)</td>
<td>77 (12-142)</td>
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<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>64 (45)</td>
<td>296 (85)</td>
<td>76 (77)</td>
</tr>
<tr>
<td>Other</td>
<td>76 (55)</td>
<td>50 (15)</td>
<td>22 (23)</td>
</tr>
<tr>
<td>CMV serostatus, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pos</td>
<td>86 (62)</td>
<td>179 (52)</td>
<td>47 (48)</td>
</tr>
<tr>
<td>Neg</td>
<td>54 (38)</td>
<td>167 (48)</td>
<td>51 (52)</td>
</tr>
<tr>
<td>Diagnosis, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AML</td>
<td>73 (52)</td>
<td>177 (51)</td>
<td>52 (53)</td>
</tr>
<tr>
<td>ALL</td>
<td>51 (36)</td>
<td>106 (31)</td>
<td>28 (29)</td>
</tr>
<tr>
<td>MDS</td>
<td>16 (12)</td>
<td>63 (18)</td>
<td>18 (18)</td>
</tr>
<tr>
<td>Presence of minimal residual disease — no./total no. (%)</td>
<td>45/137 (33)</td>
<td>104/331 (31)</td>
<td>35/90 (39)</td>
</tr>
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</table>

**Survival Analysis:**

- **CBT:** 71%
- **MURD:** 63%
- **MMURD:** 49%

**Survival Curve:**

- Observed CBT
- Adjusted CBT
- Observed MURD
- Adjusted MURD
- Observed MMURD
- Adjusted MMURD

**N at Risk:**

- CBT: 140, 73, 36, 13, 4
- MURD: 344, 170, 95, 39, 11
- MMURD: 98, 39, 28, 16, 6

**Survival Analysis:**

- **CBT:** 67%
- **MURD:** 40%
- **MMURD:** 20%

**Survival Curve:**

- Observed CBT
- Adjusted CBT
- Observed MURD
- Adjusted MURD
- Observed MMURD
- Adjusted MMURD

**N at Risk:**

- CBT: 45, 22, 9, 2, 1
- MURD: 104, 35, 25, 12, 3
- MMURD: 35, 7, 6, 3, 1
Seattle Experience Since COVID Pandemic

- Number of allogeneic transplantations decreasing with priority given to high-risk patients.

- Number of CBT decreasing but still considered as valuable option if high-risk of relapse.

- Some concerns to utilize CBT due to a presumed higher risk of Covid-19 complications. Thankfully we have not had any transplant patient infected by Covid-19.

- We have not had any issue with CB shipments.

- All patients undergoing CBT since pandemic are from ethnic minorities.
Considerations

➢ Cord Blood is a powerful source of cells (not only stem cells) and provides a platform for novel cell and gene therapies.

➢ We have not yet realized the full potential of CBT.

➢ Outstanding clinical outcomes cannot be ignored especially in high-risk patients & ability to readily transplant minorities.

➢ Expertise matters. The fact that many centers have abandoned CB is a major concern. IT IS IMPOSSIBLE TO GAIN EXPERTISE WITHOUT EXPERIENCE.

➢ Scientific publications & efforts led by the CB SIG (eg the guidelines initiative) are not sufficient to save the field.
Future of Umbilical Cord Blood Banking and Transplantation Perspectives

John E. Wagner MD
Director, Institute for Cell, Gene and Immunotherapies
University of Minnesota
The COVID19 pandemic is the greatest threat to public health & the global economy.

CB is a cryopreserved pristine source of HSC for all patients. Its loss as a stem cell source risks disenfranchising racial & ethnic minorities from potentially curative transplant treatment.

CB contains various immune effectors & other cell populations that could be used to treat cancers and infectious diseases including COVID19.

But CB is threatened by COVID19.
<table>
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<tr>
<th>Young patients</th>
<th>8/8 URD match rates falling</th>
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<tbody>
<tr>
<td></td>
<td>• 54% if patient &gt; 60 yrs</td>
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<tr>
<td></td>
<td>vs</td>
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<td></td>
<td>• 34% if patient &lt; 20 yrs</td>
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<table>
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<tr>
<th>Young donors</th>
<th>More likely to have unique HLA type</th>
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<tbody>
<tr>
<td></td>
<td>less likely to match any patient.</td>
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<tr>
<td></td>
<td>• 48% new donors &lt; 35 yrs.</td>
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<tr>
<td></td>
<td>• 60% if Asian/ Hispanic.</td>
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<tr>
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<td>• 78% if Black.</td>
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Access to HLA-matched URDs is projected to decline

Need to optimize CB transplants.

Data courtesy of NMDP Be the Match, 2018
The COVID-19 pandemic is the greatest threat to public health & the global economy.

CB is a national resource particularly during national crisis periods - radiation accidents, dirty bombs, and pandemics - impacting the collection of blood and marrow.

The CB Inventory must be preserved & the ability to do CBTs maintained & supported.
Strategies to Consider

Maximize the Availability of High Quality CB Units

Continue to support collections in high quality CBBs

&

In the event of CBB closures, consolidate high quality units by transferring them to another qualified CBB.
Strategies to Consider

Identify a Demonstration Project to optimize the conduct of CBT.

Aim is to **enhance access to CBT** & **improve transplant success** with a specific focus on serving racial & ethnic minorities & patients with high risk disease.

Propose coordinate through ASTCT
Requires coordinated efforts of ASTCT, HHS, NMDP, CIBMTR combined with funding of dedicated transplant centers