Sang de cordon
État des lieux et perspectives

E. Baudoux

20/12/2016
Importance of HLA-C

Heterogeneity of inventory

CD34 recovery associated with banking practices

Haplo identical transplants

US FDA licensure

CB comparable to BM (Children)

CB comparable to BM (Adults)

FACT-NetCord Standards 1st edition

FACT-NetCord Standards 5th edition

FACT-NetCord Standards 6th edition

Total number of cord blood units

Number of HPC Cords provided by the continents

SCI paper
SITUATION INTERNATIONALE
Number of unrelated HPC donations provided globally from 1997 till 2015
Global CBU shipments

Number of CBU shipments

SCI paper
CBU shipments WHO region Europe

Number of CBUs shipped

SCI paper
Multiple Cord Transplants are Declining at a Faster Rate than Single Cord
There Appears to be a Transition from Cord Blood to Haploidentical Transplant

Trends in CBU and Haploidentical HCT ≥ 16 years

Cau CBU  Cau Haplo  AA CBU  AA Haplo

SCI paper
The Greater the TNCC, the Higher the Likelihood of Utilization

FYTD August 2016
Goal of Interviews

• Understand reason(s) for decrease in use of cord blood as a graft source
• Understand if this decrease is temporary or permanent
• If an increase in haplo transplants is a reason for the decrease in cord blood, understand the reason for that preference
• Determine if anything would influence transplant centers to utilize more cord blood again
Selection

- Reviewed cord blood usage in US transplant centers
- Looked at use over past 5 years
- Looked for those TCs with largest decreases in the past year – looked at numbers and percent
- Interviewed 17 TCs – Dr. Linda Burns
Cord Blood Bank Technology Survey

E. BAUDOUX
M. JÖRIS

Accès public: https://share.wmda.info/display/WMDAREG/Database
73 responding banks - 30 countries

North America 18 242,735
Western Europe 15 95,520
Eastern Europe 3 13,419
Southern Europe 15 67,665
Western Asia 4 13,810
Eastern Asia 3 33,013
South Eastern Asia 2 12,436
Southern Asia 3 34,355
Northern Europe 2 7,241
Central America 1 1,690
South America 7 11,704

SCI paper
73 responding banks

76% of inventory

Responding banks

- North America: 76% of inventory
- Western Europe: 18
- Southern Europe: 13
- Oceania: 6
- Eastern Asia: 6
- Western Asia: 3
- Eastern Europe: 2
- South Eastern Asia: 2
- South America: 2
- Northern Europe: 1
- Central America: 0

SCI paper
Accreditations and State license

- **Both (FACT+AABB)**: 3 banks
- **FACT Only**: 30 banks
- **AABB only**: 9 banks
- **None**: 26 banks

<table>
<thead>
<tr>
<th>Service</th>
<th>Yes</th>
<th>No</th>
<th>In process</th>
<th>None</th>
</tr>
</thead>
<tbody>
<tr>
<td>FACT and/or AABB</td>
<td>42</td>
<td>26</td>
<td>5</td>
<td>48</td>
</tr>
<tr>
<td>Registry audit</td>
<td>45</td>
<td>15</td>
<td>13</td>
<td>25</td>
</tr>
<tr>
<td>CA license</td>
<td>63</td>
<td>10</td>
<td>7</td>
<td>11</td>
</tr>
<tr>
<td>CA inspection</td>
<td>55</td>
<td>7</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>ISO</td>
<td>48</td>
<td>25</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
WHO Region Europe Cord Blood Units added to the global database in 2015
EU Countries that have stored new CBUs in 2015

<table>
<thead>
<tr>
<th>Country</th>
<th>Number of CBUs added in 2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spain</td>
<td>2,538</td>
</tr>
<tr>
<td>UK NHS and Anthony Nolan</td>
<td>(1,170 + 934 = 2,104)</td>
</tr>
<tr>
<td>Belgium</td>
<td>1,140</td>
</tr>
<tr>
<td>France</td>
<td>910</td>
</tr>
<tr>
<td>Germany and Düsseldorf</td>
<td>(842 + 769 = 1,611)</td>
</tr>
<tr>
<td>Cyprus</td>
<td>550</td>
</tr>
<tr>
<td>Italy</td>
<td>494</td>
</tr>
<tr>
<td>Sweden</td>
<td>366</td>
</tr>
<tr>
<td>Bulgaria</td>
<td>145</td>
</tr>
<tr>
<td>Netherlands</td>
<td>138</td>
</tr>
<tr>
<td>Poland</td>
<td>69</td>
</tr>
<tr>
<td>Czech Republic</td>
<td>40</td>
</tr>
<tr>
<td>TNC</td>
<td>% in BMDW</td>
</tr>
<tr>
<td>------</td>
<td>-----------</td>
</tr>
<tr>
<td>&lt;90</td>
<td>32</td>
</tr>
<tr>
<td>90-124</td>
<td>35</td>
</tr>
<tr>
<td>125-149</td>
<td>15</td>
</tr>
<tr>
<td>150-199</td>
<td>13</td>
</tr>
<tr>
<td>200-249</td>
<td>3.2</td>
</tr>
<tr>
<td>250-299</td>
<td>0.8</td>
</tr>
<tr>
<td>&gt;300</td>
<td>0.3</td>
</tr>
</tbody>
</table>
(SÉLECTION DE LA)
LITTÉRATURE RÉCENTE
<table>
<thead>
<tr>
<th>Authors</th>
<th>Paper Details</th>
<th>Additional Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eapen et al.</td>
<td><em>Lancet oncology, 2011</em></td>
<td>Avoiding a mismatch at HLA-C in the presence of a single mismatch at HLA-DRB1 significantly lowers mortality risks</td>
</tr>
<tr>
<td>Rocha et al.</td>
<td><em>Biol Blood Marrow Transplant 2012</em></td>
<td>HLA MM CBT with NIMA match show lower TRM (A) and better OS (B) When HLA MM CBT, preferably NIMA match</td>
</tr>
</tbody>
</table>
| Eapen et al.                  | *Blood 2013*                                      | If full allele match not available:  
• 1-2 allele MM better tolerated than 3+ allele MM (10-15% difference in NRM)  
• Single MM HLA A, C, DRB1 ➔ NRM x 3 |
| Ruggeri et al.                | *Hematologica 2014*                                | Engraftment kinetics and graft failure after single umbilical cord blood               |
| Ruggeri et al.                | *Leukemia 2015*                                   | Results after UCBT and unmanipulated Haplo are likely comparable, indicating that both transplant strategies are suitable for patients lacking an HLA matched donors or when transplantation cannot be delayed |
| Saccardi et al.               | *Transfusion 2016*                                 | Cell viability assessment varied among the banks, suggesting that efforts to improve the standardization of CBU quality controls are needed |

20/12/2016
Cord Blood Graft Selection Criteria

• Cell Dose
• HLA Match
• Bank of Origin
• Processing / Cryovolume
• Other Factors

Barker et al, How I Treat, Blood 2010
Purtill, Blood 2014; Purtill et al, BBMT 2015
**Post-Thaw CD34+ Cell Recovery**

- **Overall correlation:** $r^2 = 0.73$
- **Median recovery:** 101% (range 12-1480)

**Low recovery (< 65%):** 39 CB units (11%)
- Netcord-FACT accredited: 8%
- Non-Netcord-FACT accredited: 29%

$P < 0.001$
Selecting Cord Blood Units: TNC & CD34+ Cell Dose

Total Nucleated Cells

- Single Unit: $\geq 2.5 \times 10^7$/kg
- Double Unit: $\geq 1.5 \times 10^7$/kg

CD34+ Cells

- Single Unit: $\geq 1.5 \times 10^5$/kg
- Double Unit: $\geq 1.0 \times 10^5$/kg

Post-thaw CD34+ dose can be predicted at the time of unit selection.
Cord-Blood Transplantation in Patients with Minimal Residual Disease

Filippo Milano, M.D., Ph.D., Ted Gooley, Ph.D., Brent Wood, M.D., Ann Woolfrey, M.D., Mary E. Flowers, M.D., Kristine Doney, M.D., Robert Witherspoon, M.D., Marco Mielcarek, M.D., Joachim H. Deeg, M.D., Mohamed Sorror, M.D., Ann Dahlberg, M.D., Brenda M. Sandmaier, M.D., Rachel Salit, M.D., Effie Petersdorf, M.D., Frederick R. Appelbaum, M.D., and Colleen Delaney, M.D.

In conclusion, our results showed that in patients with minimal residual disease, the use of cord blood as the donor source for hematopoietic-cell transplantation led to a higher rate of survival and a lower rate of relapse than the use of a transplant from an HLA-mismatched unrelated donor. Our data also showed that the risk of relapse was higher after receipt of a transplant from an HLA-matched unrelated donor than after receipt of a transplant from a cord-blood donor,

- **OS**: SC meilleur que donneur non apparenté HLA MM
- **Rechute**: SC meilleur que donneur non apparenté MM ou M

20/12/2016
Banking or Bankrupting: Strategies for Sustaining the Economic Future of Public Cord Blood Banks

Jeremy Magalon¹,²,³, Martin Maiers⁴, Joanne Kurtzberg⁵, Cristina Navarrete⁶, Pablo Rubinstein⁷, Colin Brown⁶, Catherine Schramm⁸, Jérome Larghero⁹, Sandrine Katsahian⁸,⁹, Christian Chabannon¹⁰, Christophe Picard¹¹, Alexander Platz¹², Alexander Schmidt¹², Gregory Katz¹ *

Conclusion

Our study shows that the utilization rate of CBUs is paramount to the economic sustainability of public banks. We found that a swift transition from strategy A to C can play a vital role in preventing public banks worldwide from bankrupting. We also found that a pre-freezing level of $18 \times 10^6$ TNC would be a cost-effective strategy to deliver therapeutic value to patients with a minimum financial deficit for the bank. In a context of limited public spending on health systems, banking decisions based on stronger selection criteria are essential if public banks are to remain financially sustainable and maximize their long-term therapeutic value for patients.
Réduction des capacités de prélèvement

• France
  – Limitation du développement du RFSP

• Finlande
  – Arrêt des prélèvements en 2014
  – Activités de la banque limitée à la distribution
  – Décision de fermer la banque en suspens (coût/bénéfice défavorable)

• Belgique
  – Pas de stratégie de recrutement coordonnée au niveau national
  – Leuven: réduction drastique du nombre de maternités (20+ ➔ 1)
  – Liège: stockage de +/- 200 unités/an

20/12/2016
Réaménagement des inventaires

• Mise à jour des critères de qualité et sélection des unités éligibles pour transplantation
  – TNC, CD34, typage,…
  – Complément de typage/tests si nécessaire

• Suppression des unités inéligibles
  – Données
  – Destruction?

20/12/2016
Attentes des utilisateurs

• À paraître dans BBMT

Consensus de 6 centres US à haut niveau d'expertise: MSKCC, Duke, U of Mn, Boston, FHCRC, MDA

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Specification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Match</td>
<td>8 allèles</td>
</tr>
<tr>
<td>Dose TNC</td>
<td>1</td>
</tr>
<tr>
<td>Match</td>
<td>2</td>
</tr>
<tr>
<td>Dose TNC</td>
<td>&gt;2.5 x10^7/Kg</td>
</tr>
<tr>
<td></td>
<td>5 x10^7/Kg si match 4/6</td>
</tr>
<tr>
<td>Dose CD34</td>
<td>1-2 x10^6</td>
</tr>
<tr>
<td>Banque d'origine</td>
<td></td>
</tr>
<tr>
<td>Accréditation</td>
<td>Obligatoire</td>
</tr>
<tr>
<td>RBC replete</td>
<td>NO (5/6)</td>
</tr>
<tr>
<td>Segment</td>
<td>Obligatoire</td>
</tr>
<tr>
<td>Délai</td>
<td>1-3 semaines</td>
</tr>
</tbody>
</table>

20/12/2016
BMT CTN Protocol 1101

A Multi-Center, Phase III, Randomized Trial of Reduced Intensity(RIC) Conditioning and Transplantation of Double Unrelated Umbilical Cord Blood (dUCB) versus HLA-Haploidentical Related Bone Marrow (Haplo) for Patients with Hematologic Malignancies

- Protocol Synopsis, version 7.0 dated January 7, 2015
- Protocol, version 7.0 dated January 7, 2015
- Summary of Changes from version 6.0 to 7.0
- Informed consent and assent, version 7.0 dated January 7, 2015
- Participating Centers
- Frequently Asked Questions
- This study is posted on clinicaltrials.gov as NCT01597778
- Cost-Effectiveness Analysis (CEA) Companion Substudy
  - CEA Overview
  - CEA Quick Reference Guide and Patient Faxes
  - CEA FAQs
  - CEA Protocol, version 4.0
  - CEA Summary of Changes from version 3.0 to 4.0

- Key Personnel
  Protocol Co-Chair: Ephraim Fuchs, MD (410-955-8143) fuchsep@jhmi.edu
  Protocol Co-Chair: Paul O'Donnell, MD, PhD (206-667-1968) podonnel@fhcrc.org
  Protocol Co-Chair: Claudio Brunstein, MD (612-625-3918) bruns072@umn.edu
  Protocol Officer: Mary Eapen, MD (414-805-0700) meapen@mcw.edu
  Protocol Coordinator: Kate Bicket (301-251-1161) kbickett@emmes.com
  Protocol Coordinator: Achintya Jaitly (301-251-1161) ajaitly@emmes.com
  Medical Monitor: Angie Smith smith719@umn.edu
Projet Fit CB panel

• Inspiré du fit donor panel (Anthony Nolan)
• Sélectionner
  – 50 000 Unités de SC
  – Banques accréditées
  – Réaliser les typages complémentaires
  – Établir un "pro-engraftment score"
    (typage HR, NIMA, KIR, IPA)
  – Établir un protocole d'essai clinique prospectif pour mesurer l'effet GVL de greffons

20/12/2016
Standards FACT-Netcord

- Standards de référence  
  ✔️ 6e édition

<table>
<thead>
<tr>
<th>Test</th>
<th>Unrelated Specification</th>
<th>Related Specification</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fresh Post-Processing</td>
<td>Fresh Post-Processing</td>
</tr>
<tr>
<td></td>
<td>Sample</td>
<td>Sample Prior to</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Release</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Post-Thaw Attached</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Segment or</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Representative Sample</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Prior to Release</td>
</tr>
<tr>
<td>Total nucleated cell count</td>
<td>≥ 5.0 x 10⁹</td>
<td>Enumerated</td>
</tr>
<tr>
<td>Total nucleated cell recovery</td>
<td>Should be ≥60%</td>
<td>Should be ≥60%</td>
</tr>
<tr>
<td>Total viability</td>
<td>≥ 85%</td>
<td>≥ 70%</td>
</tr>
<tr>
<td>Viable CD34 count</td>
<td>≥ 1.25 x 10⁹</td>
<td>≥ 70%</td>
</tr>
<tr>
<td>Viability of CD34 cells</td>
<td>≥ 85%</td>
<td>≥ 85%</td>
</tr>
<tr>
<td>Viability of CD45 cells</td>
<td>≥ 40%</td>
<td>≥ 40%</td>
</tr>
<tr>
<td>CFU (or other validated potency assay)</td>
<td>Growth (or positive result for potency)</td>
<td>Growth (or positive result for potency)</td>
</tr>
<tr>
<td>Sterility</td>
<td>Negative for aerobes, anaerobes, fungus</td>
<td>Negative for aerobic and anaerobic bacteria and fungi – OR – identify and provide results of antibiotic sensitivities</td>
</tr>
<tr>
<td>Donor screening and testing</td>
<td>Acceptable as defined by Applicable Law and NetCord-FACT Standards</td>
<td>Acceptable as defined by Applicable Law and NetCord-FACT Standards</td>
</tr>
<tr>
<td>Identity</td>
<td>Verified</td>
<td>Verified</td>
</tr>
</tbody>
</table>

There should be evidence of potency by CFU or other validated potency assay on a fresh post-processing sample.
Conditionnement


20/12/2016
The NetCord Foundation

- Fusion avec le CBWG de la WMDA
- Sont maintenus:
  - Missions et valeurs
  - Liens avec organismes partenaires
- À partir du 01/01/2017
- Banques intéressées: me contacter

20/12/2016
Our Mission

The Cord Blood Association is an international nonprofit organization that promotes the work of the cord blood community for the purpose of saving lives, improving health and changing medicine.

Our members include both public and family banks and individuals in and served by the cord blood community including cord blood bank personnel, research investigators, laboratory technicians, patients, donors, regulatory officials, vendors and health care providers such as transplant physicians, obstetricians, pediatricians, nurses and midwives.
(EN GUISE DE) CONCLUSION?
Themes / Conclusions

• CB still has a role in pediatric patients and those patients without a Haplo or unrelated donor
• Need effective protocols to improve immune function engraftment of cord blood
• Need to decrease complications seen in CB tx
• Cost of graft – not the primary factor, but are starting to get questions from insurers
• Competing trials that don’t involve cord blood
• Would take an improvement in all of the above to move back to CB
Rapid Reversal of Declining Cord Blood Activity Appears Unlikely

- Transplant center “deep dive” survey reveals practice trends and perceptions
- Updated financial modeling indicates that the breakeven point for the industry is declining
- Results of comparison studies of cord vs. other therapies are years away
Future of Cord Blood

• Despite recent decreases in use Cord remains a vital and important source of cells and will likely represent 10 to 15% of unrelated transplants and 7 to 10% of all allo transplants
• Especially important in pediatric patients with non-malignant disease
• Transplant physicians will continue to make decisions that are in the best interests of their patients understanding that they may face more economic constraints within their institutions
• Outcomes data will help sort out the best therapy by disease, age and medical status
Conclusions

• In Europe the number of CB products provided has decreased from 886 (2014) to 684 (2015)
• Twelve European countries have stored new CBU in 2015 (four countries stored more than 1,000 CBUs in 2015)
• 17.3% from the CBUs globally listed have a TNC count >150*10E7

Time to rethink about the cord blood field
Hematopoietic stem cell transplantation (HSCT) has become an accepted therapy for many congenital or acquired disorders of the hematopoietic system and has seen major changes in indications and use of transplant techniques over the years.
Cord Blood Bank
An integrated system

Collection
- Recruitment and consent
- Evaluation, eligibility and donor follow up
- Inclusion and collection
- Transport of non-frozen products

Banking
- Tests
- Labeling
- Processing
- Cryopreservation

Clinical use
- Inventory management
- Batch release and listing ➔ registry
- Search management
- Release for transplantation
- Distribution
- Recipient follow-up

Fonctions
Conclusion

- Imprévisibilité et rapidité des développements
- Évolution rapide des pratiques de transplantation pas en phase avec leur validation par des données publiées (études surtout rétrospectives)
- Succès des greffes de SC soumis à une chaîne d'expertises (prélèvement ➔ processing ➔ usage clinique)
- Transplantation: recherche du meilleur greffon
- Banques: maintien du savoir-faire (prélèvement ➔ greffe) et des accréditations
Remerciements

- Lydia Foeken
  WMDA
- Merry Duffy
  NMDP-Be the Match
  WMDA CBWG