

**ADVISORY COUNCIL ON
BLOOD STEM CELL TRANSPLANTATION (ACBSCT)**

US Department of Health and Human Services

December 6, 2022

12:00–4:00 PM

Meeting Minutes

Voting Members Present: Navneet Majhail, Chair; Juliet Barker; Marcie Finney; John Levine; Filippo Milano; and Amanda Salazar

Non-voting Members Present: Sridhar Basavaraju, Nancy DiFronzo, Max Grogl, and Hanh Khuu

Designated Federal Officer (DFO): Shelley Tims Grant

INCREASING ACCESS TO BLOOD STEM CELL TRANSPLANTATION

Barriers to Access: The Transplant and Cell Therapy Ecosystem Responds!

Stella Davies, MBBS, PhD, Director, Division of Bone Marrow Transplantation and Immune Deficiency, Cincinnati Children’s Hospital Medical Center, Cincinnati, OH

The ACCESS initiative was formed to address and sustain equality outcomes for all transplant recipients. ACCESS represents a partnership between the American Society for Transplantation and Cellular Therapy (ASTCT) and the National Marrow Donor Program (NMDP). ASTCT has more than 3,000 members as a pool of expert volunteer healthcare providers.

ACCESS first met in Washington, DC, July 28–29, 2022. They propose to reduce barriers to HCT and transplantation through implementation of changes in practice and policy by active, sustained engagement of the cell therapy ecosystem. Challenges include awareness (physicians may be working with 20-year-old data); poverty; racial inequity (Black race is a predictor of survival); lack of health insurance (more than 30% of the US population is uninsured); and prospective patients being referred too late to benefit; and social determinants of health.

Post-workshop activities include: spreading the word and championing the cause, e.g., convening follow-up committee meetings. They plan two meetings per year plus telephone conferences. They will address the issues as follows:

Awareness—Brenda Sandmaier and Erica Jensen

- Up-to-date (website) and gap analysis.
- National Comprehensive Cancer Network (NCCN) guidelines and gap analysis.
- Partnerships with disease-specific groups and health-focused community organizations; starting points are MDS and SCD.

Poverty—Navneet Majhail and Jessica Knutson

- A task force will identify available psychosocial and financial resources.
- Advocacy SWAT team.
- RFP to identify obstacles to HCT/CT (private); e.g., collaborating with Kaiser Permanente.
- RFP to identify obstacles to HCT/CT (public); e.g., Medicaid variation in state coverage for HCT/CT.

Racial Inequity—Eneida Nemecek and Rafeek Yusuf

- Process-driven plan to address unmet needs of an ethnically diverse patient populations in transplant center catchment areas.
- Geographic differences in diverse populations at transplant centers.

Post-Transplant Cyclophosphamide in Mismatched Unrelated Donor Transplantation

Bronwen Shaw, MD, PhD, Chief Scientific Director, Center for International Blood and Marrow Transplant Research, Milwaukee, WI

Survival following alternative donor HCT is inferior to survival following matched HCT. In a recent trial with 80 US patients, after a fresh bone marrow graft (day 0), PTCy was administered on days 3 and 4, and sirolimus/mycophenolate mofetil on day 5. There was no new onset of GVHD after 1 year, and non-relapse mortality after 3 years was less than 10%.

More recently (September 2021 to August 2024), more than 200 patients have been recruited far quicker than predicted (which indicates the need). Donors are younger than 35 years. Of the total, 49.8% are not diverse racially and ethnically, but 45% are (5.7% were not reported). Donor characteristics used in the selection of final donors were: youth, CMV serostatus, ABO status, sex, and previous pregnancies. The initial phase 2 study showed feasibility of a PTCy-based mismatched unrelated donor approach.

Q&A

Question: Dr. Levine: How are you addressing patients who live far from a transplant center?

Answer: Dr. Davies asked that Dr. Levine email her, since they are just starting out. These are the kinds of things that need to be addressed, e.g., by using telemedicine or local physicians.

Question & comment: Dr. Auletta: One thing underutilized is county health services, e.g., public transportation. What strategies are the group considering? Transplantation can change the life of individual patients, so if even one patient benefits, it's a win. But, these are entrenched problems.

Question: Ms. Barker asked if patients' ancestry and socioeconomic status are considered—this is a huge issue.

Answer: Dr. Shaw replied that, often annual household income is not recorded.

Comment: Ms. Barker: It should be acknowledged that we have an army of staff who will help the patients, e.g., if insurance coverage is denied, staff members will get the approval. Free stays near the hospital are another service they offer; other centers may not have these options. Also, pharmacists are critical.

Question: Suzanne Pontow: Did you consider CB as a graft source? Did any of the patients have a better match with a cord blood unit, especially given that speed to access is best with cord blood?

Answer: Dr. Shaw: That all depends on the institution.

Question: Filippo Martino: Do we have data in chronic GVHD?

Answer: Dr. Shaw: After 1 year no increase in GVHD was observed; otherwise it is unknown.

CORD BLOOD: CHALLENGES AND OPPORTUNITIES

Current State of Public Cord Blood Banking in the United States

Marcie Finney, MS, MBA, Executive Director, Cleveland Cord Blood Center, Cleveland, OH

CB expands access for patients from diverse racial/ethnic backgrounds and can shorten the time to transplantation. Yet, CB transplants have been decreasing over time, while CB banks continue to add to their inventory. We want to increase the number of racially and ethnically diverse donors. The RAND Corporation reports key themes, namely, the value of having a public bank far outweighs the costs; it increases life span; and demand for CB has flattened, but competition among CB banks has increased.

An all-CB-banks meeting in August 2022 concluded with consensus proposal initiatives:

- Maintain the inventory (supply).
- Remove N20 mandatory racial accrual caps.
- Reevaluate racial classifications.
- Align reimbursements with current costs.
- Advocate with FDA for removal of certain restrictions for donor eligibility.
- Extend delivery.

To increase CB utilization (demand), we should facilitate use of CB in HSCT, establish initiatives to quantify long-term outcomes of CB transplants, and support use of CB in cell and regenerative therapies. Attributes include: expense control, inventory growth, and distance to other banks.

To move forward, CB banks must increase utility, maintain inventory, conduct research and development, advance new products (e.g., Gamida Cell's Omidubicel), get FDA licenses, maintain diverse collections, and ensure good manufacturing practices. Importantly, they must tell people's stories.

Trends in Utilization of Cord Blood for Hematopoietic Stem Cell Transplantation

Juliet Barker, MBBS, Director, Cord Blood Transplant Program, Memorial Sloan Kettering Cancer Center, New York, NY

The goal of the Cord Blood Transplant Program is to provide effective HSC sources for transplantation of all patients at the optimal time for patient care. Outcomes of CBT are improving, but outcomes are contingent on the center's expertise—unit selection, conditioning, letermovir administration, and early post-transplant care. CBT now has improved access, faster

transplantation, low chronic GVHD, low relapse, improved racial equity, good outcomes, cost savings, and improved quality of life.

However, multiple problems explain why CB transplantation did not increase during the pandemic. CBT biology has been poorly understood and research funding limited. Despite having HRSA-funded CB inventory, too few transplant centers know how to use it. Access to haplo-identical donors is not universal. Recipient donor-specific HLA antibodies imply high relapse rates with a PTCy platform because there is no reliable desensitization strategy (two or more pregnancies are a problem). Problems were compounded by centers not collecting inventory during COVID-19.

Recommendations:

- Maintain domestic inventory of high quality and high cell content units.
- Analyze how many patients undergoing a formal search were transplanted with an adult donor, and what happened to those who were not.
- Improve efficiency of patient and donor assessment and have CBT as an alternative.
- Support training in CBT in transplant centers nationally.
- Fund a national CB network led by transplant physicians who will optimize CBT access and outcomes with a focus on minority patients and high-risk disease.

Cord Blood Expansion Technologies

Filippo Milano, MD, PhD, Director, Cord Blood Transplant Program, Fred Hutchinson Cancer Research Center, Seattle, WA

Delayed engraftment in CBT delays hematopoietic recovery. Promising technologies to overcome engraftment delay include: notch-ligand universal donor (off-the-shelf); nicotinamide; and UM171 molecules.

Manufacturing processes for CD34⁺ cord blood is not just an expansion but a new graft, which engrafts faster, thereby reducing GVHD to low moderate or severe chronic GVHD, which consequently lowers risk of transplant-related mortality.

Engraftment and primary graft failure are no longer a barrier in myelo-ablative CBT. Graft manipulation must be simplified in all its utilization to reduce the time it takes. However, although graft manipulation remains important, it is no longer needed to enhance recovery. We have not yet realized the full potential of CBT.

Q&A

Question: Machi Scaradavou: Since CB transplantation attributes—namely, equal access for all independently of race, prompt treatment, and excellent outcomes—align perfectly with “equal outcomes for all,” how will ASBSCT and NMDP promote CB utilization?

Answer: Dr. Auletta: From the NMDP standpoint, several guidelines have been published and we continue to collect data and supply CB.

Question: Ms. Finney asked about concentrates. They get requests for CB units, but mostly see patients who are ready to proceed. As a clinician, how do you proceed?

Answer: Ms. Barker: A variety of aspects are determinants in answering this question. With a diverse patient population, CB is an option. The demand for haplo-identical has dropped off, but for mis-matched has picked up. Nimbleness of staff who select the units is important.

Question: Dr. Majhail: You publish on access to transplants, but how much of your experience in your center reflects what happens in the country as a whole, i.e., in all seven transplant centers. His center does about 15 transplants/year, mostly in children, and there's been a decline. Most patients who drop off do so, not because there is no donor, but because their disease status doesn't allow transplantation. Is there data on this?

Answer: Ms. Barker: We have no data, but we need it. This is an intention-to-treat issue. Maybe the best standard of care is to take the patient to transplantation within 2 weeks, but often CB is not available, but, if you wait, the disease can progress so you miss that window of opportunity.

Comment: Steven Devine: Ms. Finney, Ms. Barker, and Dr. Milano have made a strong case for protecting CB as a vital source for patients who may benefit. NMDP fully supports maintaining the availability of CB grafts. Demand for grafts and actual type of donor chosen should be left with the transplant center teams because they know their patients best. This is something NIH and other funding organizations can address.

Question: Dr. Majhail: The lack of people who focus on CBT has been made clear. What are the challenges? You have dedicated fellows. What are the barriers?

Answer: Ms. Barker: Some were interested and came to her clinic, but lately CBT is not new and special, so it doesn't attract new clinicians. We need to make CB sexy again.

Comment: Amy Ronneberg: Data from CIBMTR and operational data support Dr. Majhail's comment: The majority of patients drop out due to medical-related issues. We track the requests from transplant centers for every requested CB donor and the timing is similar, so one product is not being used to take patients to transplantation faster. It is surprising that we are not seeing CBT being used to take patients to transplant faster across the country.

PUBLIC COMMENTS

None

NEW BUSINESS AND CONSIDERATION OF RECOMMENDATIONS

Dr. Majhail summarized. Over the last 2 days' discussion, three topics became clear: drug shortages, COVID-19, and CB inventory and access to transplantation. We should distinguish between patients with leukemia and those with SCD; i.e., acute vs elective need. *Dr. Rizzo* agreed, adding that there was no differential effect of COVID at centers for either. Then there are psychosocial aspects and time to transplant.

Drug Shortage

Drs. Levine, Barker, and Majhail thought government needs a strategic policy to ensure the supply of drugs. *Ms. Barker:* We can't get the drug because its not available, or because we can't get it in the United States. We need to address the process for drug approval. She suggested that

expert transplant physicians go to FDA and explain the need. *Dr. Levine*: FDA is looking at its options; we don't need a new process.

Ms. Finney suggested forming a subcommittee. *Dr. Majhail* agreed. *Dr. Levine* nominated *Dr. Maziarz* to chair the subcommittee; we need a representative from FDA. How do we address any future drug shortages? How do we deal with stakeholders? Would it be worth exploring whether production can be increased?

COVID

Dr. Auletta: The clear and real danger is COVID and the shortage of effective drugs.

Dr. Majhail agreed and suggested that we contact the Secretary of the Department of Health and Human Services (HHS). Can NIH direct RFAs and program announcements to this area? We should advocate for more NIH funding to address these issues. Center outcomes were not impacted by COVID. But, countered *Ms. Barker*, access and COVID will rapidly collide.

Dr. Levine: What about the survival impact and control of the pandemic, e.g., lock-downs? But, that's not virus-specific; it could be any pandemic.

Access

Ms. Barker was interested in an initiative led by patient advocates, totally independent of transplant centers. There are many issues here. How would the patients address donor access and other aspects? This council is supposed to have a patient advocacy representative, and there are patient advocacy organizations. We should focus at a high level on access. What can we do to support centers so they can do what they do better? Distance from a transplant center is one problem. Issues that need more considerations include temporary licenses to practice in other states, and virtual meetings.

CONCLUSIONS

Dr. Majhail summarized the issues as: access, utilization, CB inventory, and COVID.

Dr. Auletta thought the biggest thing for HRSA is continued awareness based on existing need. There must be a multi-pronged approach, and for that, agencies must be informed.

Nancy DiFronzo pointed out the need to bring into the access group the Centers for Medicare and Medicaid Services (CMS) to make them more aware of the issues.

ACTION ITEMS

1. Council members will talk off-line to clarify the opportunities.
2. Two subcommittees—Food and Drug Administration (FDA) and Drug Shortages, and Cord Blood Transplantation and Availability—will be formed immediately.

The meeting adjourned at 4:15 PM