ADVISORY COUNCIL ON

BLOOD STEM CELL TRANSPLANTATION (ACBSCT)

US Department of Health and Human Services

December 5, 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

WELCOME AND OPENING REMARKS

Navneet Majhail, MD, MS, FASTCT; ACBSCT Chair

Shelley Tims Grant, DFO; ACBSCT Executive Secretary

INTRODUCTION OF MEMBERS

Ms. Grant opened the meeting at 12:08 PM and explained that the role of the Advisory Council on Blood Stem Cell Transplantation (ACBSCT) is to advise, assist, and make recommendations to the Health Resources and Services Administration (HRSA) on the C.W. Bill Young Cell Transplantation Program (CWBYCTP), and the National Cord Blood Inventory (NCBI) Program.

Dr. Majhail noted that this is the first ACBSCT meeting convened in 2 years, and, in that time, the field has shifted toward non-transplantation therapies, including innovations to treat graft-vs-host disease (GVHD). He then introduced the five other council members—Juliet Barker, Marcie Finney, John Levine, Filippo Milano, and Amanda Salazar. He invited participants to join the Council or to recommend possible members.

UPDATE ON C.W. BILL YOUNG CELL TRANSPLANTATION PROGRAM

Division of Transplantation, Health Resources and Services Administration (HRSA)

Shannon Taitt, MPA, Chief, Blood Stem Cell Transplantation Branch

The Division of Transplantation (DoT) is the primary federal entity in the United States responsible for oversight of organ and blood stem cell transplantation systems and initiatives to increase organ, blood stem cell, and tissue donation. The Stem Cell Therapeutic and Research

Act of 2005, amended in May 2021 (i.e., the Transplant Act of 2021), authorizes the C.W. Bill Young Cell Transplantation Program (CWBYCTP), the National Cord Blood Inventory (NCBI), and Advisory Council on Blood Stem Cell Transplantation (ACBSCT). HRSA also chairs the Hematopoietic Stem Cell Transplantation (HSCT) Working Group, which meets twice a year. The CWBYCTP supports patients who need unrelated bone marrow or umbilical cord blood transplants. There are currently six NCBI contractors actively collecting and receiving financial support.

Appropriations in fiscal year 2022 exceeded $50 million. Of the 24 million adult volunteer donors, more than 4 million (~16%) are racial and ethnic minorities. Chances of patients finding a suitably matched unrelated donor vary by race and ethnicity, e.g., of the 250,000 bone marrow (BM) donors in 2022, 60% were White, 5% Black/African American, 12% Hispanic, and 8% mixed race. NCBI's goal is to contract with multiple cord blood (CB) banks to build a public inventory of at least 150,000 new, high-quality, and genetically diverse cord blood (CB) units.

Unrelated blood stem cell transplants increased from 5,946 in 2021 to 6,425 in 2022, however, transplants decreased among minority populations while they increased among White populations. Nevertheless, HRSA remains committed to adding more adult donors and CB units to the registry, as well as addressing other non-donor-related matters.

Single Point of Access—Coordinating Center

Merry Duffy, Director, Search Operations, National Marrow Donor Program, Minneapolis, MN

NMDP is renowned for its matching services and has created training modules. For continued success, it is crucial for them to maintain a wide network of partners. Marketing campaigns increase awareness and participation with a focus on young donors via NMDP's college/university strategy.

NMDP's 5-year accomplishments include:

- Recruited 1,269,949 adult volunteer donors;
- Implemented a digital donor registration system and member experience portal;
- Developed a comprehensive report of members' experiences and insights;
- Expanded national marketing campaigns to drive awareness;
- Achieved the highest donor request volumes, which impacted the most lives, both overall and for ethnically diverse patients;
- Expanded enhanced preliminary search to allow transplant physicians to vet donors before selection;
- Amended agreements with five NCBI contractors to facilitate collections from underrepresented populations;
- Focused on increasing utilization;
- Defined best practices in shipping CB; and
- Instituted staff training and process validation and produced guidelines accordingly.

Challenges include:

- Supply chain shortages as an effect of COVID-19 positivity. These shortages significantly impact the availability of collection and processing kits for many locations, and are projected to continue;
- Staffing shortages, which require many nurses to travel;
- Increased number of mothers who test positive for COVID-19 when admitted to a hospital;
- Compassion fatigue, i.e., changes in altruism post-pandemic as consumer sentiment moves to a more individualistic mindset;
- Addressing needs and supporting donors with mental health challenges; and
- Gaining consumer attention and awareness.

Office of Patient Advocacy

Mary Senneka, Program Analyst, Transplant Need, Utilization, and Outcomes, National Marrow Donor Program, Minneapolis, MN

The primary role of the Office of Patient Advocacy (OPA) is to support patients. Its patient outreach program has:

- Increased individual patient support for those who need allogeneic transplants;
- Increased interactions among caregivers, families and patients, and physicians and other health professionals;
- Gained better understanding of patients' needs;
- Aided patients in clinical trial navigation to help them find a trial that may benefit them; and
- Offered counseling services and peer connections as well as patient advocacy and case management.

With the patient navigator program, the navigator calls the patient to assess barriers and solve problems. This proactive approach has had a fantastic response as indicated by patients who have conversed with a patient navigator being 24% more likely to receive a transplant. The most commonly reported barrier (42% of patients) is financial issues. OPA offers one-on-one support, a website, financial assistance, and educational resources. With their Peer Connect Program, prospective patients can hear from others who have been through the transplantation process. Program use has increased steadily.

In addition, OPA produces educational materials for patient and healthcare professionals in English, Spanish, and 11 other languages, as well as comprehensive community hematology/oncology education via websites, webinars, podcasts, videos and print summaries, conference attendance, and local clinic operations partners. Information dissemination includes bethematch.org, and a transplant center directory that can be searched by location or disease. OPA also manages the content on the CWBYCTP website that enables patients to search risk factors, transplant types, and survival rates.

Stem Cell Therapeutic Outcomes Database

J. Douglas Rizzo, MD, MS, Senior Scientific Director, Speaker Position, Center for International Blood and Marrow Transplant Research, Medical College of Wisconsin, Milwaukee, WI

The Center for International Blood and Marrow Transplant Research (CIBMTR's) Stem Cell Therapeutic Outcomes Database (SCTOD) collects, analyses, and disseminates data from both related and unrelated donors. Its three contractors work closely together and with HRSA. They are involved in continuous process improvement programs, and their on-site audit program is essential to maintaining data quality. Nearly all (90–95%) of the 175 US centers are in good standing. CB quality reports have been produced for more than a decade and are available to European and non-European banks as well as our own. The Cybersecurity and Data Privacy Program also ensures integrity of data and its accessibility by only a select group.

It is essential to share the data among the centers; it can be used for center performance analysis, requests for information (RFI), the PartnerShare platform, or publications. In addition, SCTOD offers a financial payments tool to understand reimbursement, and a data operations dashboard to facilitate knowing what data are due to whom and when. Publication of analytic datasets involves de-identification of datasets. Corresponding data dictionaries were begun in July 2019.

CB transplantation is being replaced by haplo-identical-cord transplantation, which combines infusion of an umbilical CB unit with CD34-selected cells. Outcomes of transplantation in the era of COVID indicate that time varying COVID effects were not significant across US transplant centers.

Q&A

Question: Marcie Finney: How did the investigator increase use?

Answer: Ms. Duffy said that to increase use they improved the ability to search reports and provided consultation services free of charge.

Question: A participant asked whether transplant research is available to anyone.

Answer: Ms. Senneka said its availability is listed on the NMDP website.

COVID-19: IMPACT ON BLOOD STEM CELL TRANSPLANTATION, DONATION, AND OUTCOMES

Effects of the COVID-19 Pandemic on the Hematopoietic Cell Transplant Ecosystem

Jeffery Auletta, MD, Senior Vice President and Chief Scientific Director, National Marrow Donor Program, Minneapolis, MN

High-quality data can guide clinical practice. The focus here was on unrelated hematopoietic cell transplantation (HCT) outcomes regarding donor, product, and patient. Common themes that emerged were: adaptability, advocacy, communication, partnership, and donor and patient safety.

Challenges around SARS-CoV-2 infection include: incomplete vaccination, sequelae (long-term COVID, and multi-inflammatory syndrome in children); and emergence of variants of concern

and immune escape. Studies undertaken in 2021 showed that recipients had no response to SARS-CoV-2^{+} donors' blood. However, donor availability remains a challenge because of breakthrough and *de novo* infections, compassion fatigue, and misinformation and mistrust. Demand for young and ethnically diverse donors remains a challenge.

Challenges for patients include: impact of long COVID-19; limited prevention and therapies in a context of new variants; and concomitant respiratory viral infections, including respiratory syncytial virus (RSV) and influenza. They need COVID-19 relief funds. NMDP is involved in advocacy through lobbying and letter-writing recommending boosting and revaccination and has also developed collaborative guidelines.

Conclusions:

- SARS-CoV-2 is the new norm and we will likely need yearly boosters for at least 5 years.
- Breakthrough infections with the emergence of new variants and their reservoirs are to be expected.
- Respiratory viral infections will remain a significant cause of morbidity and mortality in allogeneic HCT.
- Immunocompromised patients will remain at risk for severe COVID-19.
- With the dearth of preventive and therapeutic options, collecting and analyzing infection data are critical to guiding clinical practice and improving patient outcomes.

Center-specific Survival Analysis and Handling COVID-19

J. Douglas Rizzo, MD, MS, Senior Scientific Director, Speaker Position, Center for International Blood and Marrow Transplant Research, Medical College of Wisconsin, Milwaukee, WI

The premise of risk adjustment is that different centers have different case-mix distributions, which affects outcomes. Therefore, in 2021, CIBMTR undertook a Center-Specific Analysis (CSA) to understand the impact of practices developed during the COVID pandemic, e.g., seeing patients virtually. Patients who developed COVID infection were censored from survival analysis on infection date.

In CSA 2021, three time-varying COVID affects were studied—calendar time period; average COVID infection rates (per 100,000) over the preceding 2 weeks based on the zip code of the transplant center; and average COVID death rates over the preceding 2 weeks based on the zip code of the transplant center. They looked for interactions of the three variables with themselves and for acute or chronic GVHD. No independent effect of the COVID pandemic was demonstrated to impact care delivery and no interaction was seen.

Additional information was collected on how COVID affects transplantation. Data from ~80% of centers indicated that only 30% had a change in approach and that was mostly date or use of cryopreservation. Analysis of time-fixed effects or time-varying effects indicate that neither was significantly associated with 1-year mortality with or without censoring for post-HCT COVID infection.

COVID-19 National Guidelines and Clinical Trials in Blood Stem Cell Transplantation Recipients

Joshua A. Hill, MD, Assistant Professor, Vaccine and Infectious Disease Division, Fred Hutchison Cancer Research Center, Seattle, WA

Bone marrow transplantation (BMT) patients are at high risk for severe/fatal COVID-19 complications. About 3% of US and Canadian populations are immunocompromised, i.e. ~11 million people. But, optimal management is unknown, e.g., whether we should be using longer duration of treatment or combinations of treatments.

Other unknowns include:

- Serologic thresholds that correlate with protection;
- When to restart the primary vaccination series;
- Clinical trials for HCT recipients and immunocompromised;
- Whether neutralizing antibody responses to wild type, delta, and omicron strains differ.

To define dose, duration of immunity, and effectiveness, it is essential to include immunocompromised patients in vaccine trails for pandemics and emerging infections. This would include a specific focus on immunocompromised patients and specific research funding. Public–private collaborations are important for developing and maintaining access to therapies for "orphan" populations, and industry should have a parallel or post-marketing vaccine development.

Q&A

Question: Dr. Majhail asked whether racial/ethnic disparities were seen in availability.

Answer: Erica Jensen replied that NMDP has seen the biggest decrease in availability among young, White donors. She attributes this to compassion fatigue and to an unwillingness or inability because of restrictions to help a stranger. NMDP has changed its messaging in response to these issues.

TRANSPLANTATION AND GENE THERAPY FOR SICKLE CELL DISEASE

Update on Blood Stem Cell Transplantation for Sickle Cell Disease

Shalini Shenoy, MD, Director, Pediatric Stem Cell Transplant and Cellular Therapy Program, Washington University, St Louis

Sickle cell disease (SCD) occurs worldwide and in some 100,000 people in the United States. Patients with contributory conditions are often referred for transplantation. HLA-matched sibling donors are ideal, but availability is less than 20%. So, matched and mismatched, unrelated donors are used; CB is an alternative. A prospective donor must be medically able to donate. Criteria include age, HLA antibodies, rejection risk, and infection risk. Both CB and BM yield excellent outcomes; peripheral blood (PB) is worst. Survival exceeds 89% (death is due to organ failure, GVHD, or infection). Patients younger than 4 years show good survival, but that

decreases with age. New SCD-related events arise in those older than 16 years. Organ dysfunction is significantly higher. Growth hormone deficiency and gonadal dysfunction incidence continues to be a risk, as does GVHD, which occurs in 33% of patients.

Abatacept is used as prophylaxis against GVHD. Engraftment improves with total body radiation and reducing intensity of regimen. Newer intervention trials have been undertaken with post-transplantation cyclophosphamide (PTCy) + abatacept without radiation. Progress is indicated by 87 to 90% survival after 2 years. Benefits of transplantation include early amelioration of acute pain episodes, although chronic pain is more complex; stable pulmonary function; stabilization/improvement in renal function; and quality of life (QOL), e.g., shorter hospital stays, which decrease health care costs.

There is a 4% chance of malignancy after graft rejection within 2 to 5 years in young adults. The degree of improvement that can be expected after HCT depends on the extent of disease and treatment-related morbidity. End-point parameters must be followed long-term for disease-related outcomes and transplant-related toxicities and depend on age, disease severity, transplant method, and donor.

Transplantation for SCD is improving in all areas. Follow-up studies reveal the importance of decreasing intensity and toxicity. For the long-term, registries must focus on critical aspects to enhance CIBMTR data banks. It is also critical that medical teams, recipients, and families understand expectations and the pros and cons of HCT.

Developments in Gene Therapy for Sickle Cell Disease

Haydar Frangoul, MD, Director, Sarah Cannon Pediatric Hematology/Oncology & Cellular Therapy at TriStar Centennial, Nashville, TN

Gene therapy, either gene addition or gene editing, is a curative option for sickle cell disease (SCD); the biggest problem is finding a donor. Best results have been achieved with HLA-identical sibling, but unrelated donor transplant, haplo-identical transplant, and gene therapy are also options.

Gene editing involves gene disruption and gene correction to enable precise changes in the DNA. Gene addition begins with apheresis and $CD34^+$ hematopoietic stem and progenitor cells with lentiviral vector encoding. Human pluripotent stem cells (HPSCs) are transduced with the BB305 lentiviral vector encoding a modified β-globin gene.

Currently under investigation is fluorescence *in situ* hybridization (FISH), which shows trisomy 8 and a high degree of polyclonal reconstitution. Most recipients were pain- and hospital-free at 3 years. Ongoing trials of Exa-cel—a cell therapy that uses non-viral, *ex vivo* CRISPR/Cas9-mediated editing of *BCL11A* to increase HbF levels—yield a safety profile consistent with that of busulfan myeloablation and autologous HSCT.

With gene therapy, there is no need for a donor and no risk of rejection or GVHD. But, the approaches may not be curative; high-dose chemotherapy is needed with consequent risk of infertility and secondary malignancy. Moreover, it cannot be offered in resource-poor countries.

Black/African American Recruitment—Highlighting Sickle Cell

Erica Jensen, Senior Vice President, Member Engagement, Enrollment, and Experience, National Marrow Donor Program, Minneapolis, MN

The Black American population is concerned about being treated fairly and with respect in the health care environment; at the same time they must understand the risk. NMDP provides a detailed timeline of the process, intended use, costs, etc.

The Telling Black Stories program in the paid media, e.g., a national podcast called "Black Blood Heals," and other public relations efforts and social media are all about sharing awareness of access. NMDP is executing an integrated marketing community plan and presence in relevant media. Their goal is to enlighten and inform Black Americans about existing disparities, and to empower Black Americans with the knowledge that they themselves are the cure. NMDP aims to inspire them to learn more about and engage with Be The Match, the goal being to save lives.

Multiple media are used: events, TV, paid social media, online video, and podcasts. Cultural holidays and months continue increasing brand awareness as do digital media, dedicated landing pages, social media, and campus events. For example, Sickle Cell Awareness Month campaigns increase awareness of the disease and the possibility of BMT. A signature event was Cheek Week (an event to increase the BM registry). Thanks to such events, awareness has increased by more than 70%. They are building partnerships for community connections via their Game Program, Patient Engagement Program, Volunteer Program, and partnerships, and by involving Historically Black Colleges and Universities (HBCUs). All these activities come under the umbrella of Operation Save Our Selves (SOS). Developed by Black ERG, this is a sustainable movement, not just a campaign. It involves Black African American partnerships including: 23 HBCUs' paid internship programs; daily presence on campus of Be The Match representatives; peer-to-peer engagement; and integration.

Q&A

Comment: Dr. Shenoy noted that searches are open. The advent of CB extension changes how we think about cell dose, which is attractive. Another issue is the cost of the product as well as having a back-up in case of graft rejection. Risk of GVHD is much different for CB than for other sources. But, pediatric patients are still in a better position than adults.

Comment: Dr. Frangoul noted multiple ongoing trials. Products will be coming to the market that prevent graft rejection. The field is moving so fast that he hopes to see that every patient has an option.

Question: Dr. Levine: Will the cost of ~$2 million impact our ability to bring a cure to patients?

Answer: Dr. Frangoul thought it would; we have to wait and see how third-party payors, especially public payors, react. And, we have to see how the products will be priced. We must support the patient throughout the process (~6 months).

DRUG SHORTAGES IN BLOOD STEM CELL TRANSPLANTATION

Impact of Fludarabine Shortage in Blood Stem Cell Transplantation: Perspective from the Bedside

Richard Maziarz, MD, Director, Adult Stem Cell Transplant Program, Oregon Health and Science University, Portland, OR

Drug shortages—including chemotherapy, supportive care, antimicrobials, and supplies—are commonplace in the management of hematological malignancies, hematopoietic cell transplantation (HCT), and cell therapy patients. Because of COVID, common drugs for respiratory diseases have also been in short supply.

The shortage of fludarabine, a well-tolerated drug, is important because of its frequent use in allogeneic transplantation over the past 10 years. Some 60% of acute myeloid leukemia (AML)/myelodysplastic syndromes (MDS) patients received it, as did 21.4% of acute lymphocytic leukemia (ALL). Fludarabine is the backbone of the PTCy regimen. Moreover, fludarabine is an excellent immune suppressor. Lympho-depletion has been used in autologous cell therapy since the 1980s, and more than 90% of those treated with a lympho-depletion regimen receive fludarabine. As haplo-identical HCT and chimeric antigen receptor (CAR) T cell therapies emerge, and CB HCT evolves, demand will become more urgent.

June 2, 2022, a worldwide shortage was suddenly announced. Of the three manufacturers, two gave no reason for the shortage and one cited increased demand. At the institutional level, the shortage means deferred patient transplants. We can adjust dose delivery, use alternative regimens, etc., but the fludarabine shortage remains and challenges continue, including fludarabine pricing and increasing payer denials for care. The shortages impact patient care delivery and add massive additional administrative demands to the system.

Q&A

Question: Dr. Majhail: What might be asked of FDA regarding what you've learned from the fludarabine shortage?

Answer: Dr. Maziarz: FDA needs to know when we have a change in our community—cell immune therapy constitutes a sudden change in demand. When we see cases in our field, we need a community system to address them.

FDA's Strategy to Address Drug Shortages

Captain Valerie Jensen, RPh, Staff Director, Drug Shortage Division, US Food and Drug Administration, Silver Spring, MD

The mission of the Drug Shortage Division of FDA is to prevent, mitigate, and alleviate drug shortages. Access to life-saving medications for patients and practitioners is their #1 priority. The drug shortage staff works with professional organizations, patient groups, clinicians, and other stakeholders, and is designated to oversee and facilitate resolution of all drug shortage

situations. That includes the Coronavirus Aid, Relief, and Economic Security Act (CARES Act) of 2020.

Key collaborators include other US agencies, international authorities, manufacturers, pharmacists, patients, providers, researchers. To assist with shortages FDA can require early notification, but cannot require a company to make a specific product. FDA achieves proactive outreach through the Center for Drug Evaluation and Research (CDER) NextGen Drug Shortage Emergency Event Portal. It prompts firms to look at demand and supply.

Shortages may be new, or persistent and ongoing, and they cannot always be prevented or anticipated. Alternate manufacturers may not be able to make up the production shortfall. But, in an emergency FDA may expedite review of company proposals, or allow temporary importation with regulatory flexibility and discretion, e.g., the fludarabine shortage is being addressed by temporarily importing it from Canada.

A 2018 FDA Report identifies causes and recommendations:

Root causes:

- Lack of incentives for manufacturers to produce less-profitable drugs.
- The market does not recognize and reward manufacturers for mature equality systems that focus on improvement and early detection.
- Logistical and regulatory challenges make it difficult for the market to recover from a disruption.

Recommendations:

- High-quality management rating.
- Risk-management plans that identify vulnerabilities and proposed responses.
- Quality systems upgrade.
- Redundancy in manufacturing, and suppliers who encourage industry to have "warm lines" and components.
- More capacity.
- Communication is key in supply and in demand.

Q&A

Question: John Levine: Are there plans to move more manufacturing to the United States?

Answer: CAPT Jensen: We learned the importance of knowing where things are made and the state of existing markets, e.g., the lock-down in China. We cannot require a company to locate elsewhere.

Question: Ms. Barker: Occasionally we have an important drug that could be converted for a substantial population and has been approved in Canada and Europe, but not by the FDA, so we cannot get it in the United States. What avenues do transplant physicians have to appeal to the FDA to reconsider the decision?

Answer: CAPT Jensen: The Clinical Review Division would address that. In this case, continue to advocate for that drug. There is a personal importation option that might help. Email CAPT Jensen and she will elaborate.

Question: Max Grogl: How does FDA balance redundant manufacturing? Does that increase the price?

Answer: CAPT Jensen: Having a company or supplier that has a backup line comes with a cost. Companies make those decisions, but we don't want increased prices.

Question: Dr. Majhail: What about surprise shortages? Who must notify stakeholders?

Answer: CAPT Jensen: FDA works with companies to determine supply and demand—it's a moving target, especially if more than one firm is involved. FDA believes it is very important to get that information to stakeholders ASAP. FDA puts the information on their website, but companies warn FDA not to post it too soon because notifying of future shortage increases current demand, which exacerbates the problem.

PUBLIC COMMENTS

A public comment session was offered; however, no one

registered. The meeting adjourned at 3:54 PM