ADVISORY COUNCIL ON

BLOOD STEM CELL TRANSPLANTATION (ACBSCT)

US Department of Health and Human Services

September 28, 2023

2:00–6:00 p.m.

MEETING MINUTES

Voting Members Present: Navneet Majhail, M.D., M.S., M.B.B.S., Chair; Juliet Barker, M.B.B.S.; Ann Richardson Berkey; Marcie Finney, M.S., M.B.A.; Richard Maziarz, M.D., and Filippo Milano, M.D., Ph.D.

Nonvoting Members Present: Nancy L. DiFronzo, Ph.D., National Heart, Lung, and Blood Institute, National Institutes of Health (NIH); Max Grogl, Ph.D., Naval Medical Research Center; Frank Holloman, Health Resources and Services Administration (HRSA);

Others Present: Jeffery Auletta, M.D., Center for International Blood and Marrow Transplant Research (CIBMTR); Robert Carter, NIH; Ericka Narr, National Marrow Donor Program (NMDP); Laura Odwazny, J.D., Office of the General Counsel, Department of Health and Human Services (HHS); Elizabeth Shpall, M.D., MD Anderson Cancer Center; Jeffrey Wilson, MD Anderson Cord Blood Bank

Designated Federal Officer (DFO): Shelley Tims Grant, Executive Secretary, ACBSCT

WELCOME AND OPENING REMARKS

Navneet Majhail, M.D., M.S., M.B.B.S.; ACBSCT Chair

Shelley Tims Grant, DFO; ACBSCT Executive Secretary

Dr. Majhail called the meeting to order at 2:03 p.m. and welcomed the participants. (The meeting was held virtually and open to the public.) Dr. Majhail introduced three new committee members: Ann Richardson Berkey; Eapen K. Jacob, M.D.; and Richard Maziarz, M.D. He said the ACBSCT provides advice and recommendations to the HHS Secretary via the HRSA Administrator on the activities of the C.W. Bill Young Cell Transplantation Program (CWBYCTP), and the National Cord Blood Inventory (NCBI). The main focus of the ACBSCT is to advise HRSA on improving access and outcomes for people who need blood stem cell transplants and cellular therapies.

Dr. Majhail summarized the proceedings of the ACBSCT meeting in December 2022. The ACBSCT heard updates regarding the NCBI, CWBYCTP, the NMDP's Office of Patient Advocacy, and the CIBMTR's Stem Cell Therapeutic Outcomes Database. Presenters offered insights on the impact of the COVID-19 pandemic on blood stem cell transplantation, donation, and outcomes; the status of transplantation and gene therapy for sickle cell disease; and increasing access to blood stem cell transplantation. A discussion of drug shortages in blood stem cell transplantation prompted the ACBSCT to create a subcommittee, chaired by Dr.

Maziarz, with representation from the Food and Drug Administration (FDA), to look into the issues. That subcommittee has not yet met. As a result of a session on the challenges and opportunities in using cord blood, the ACBSCT formed another subcommittee, which met this past summer and will provide an update at this meeting. (Minutes of past ACBSCT meetings are available online.) Dr. Majhail then gave an overview of the agenda for the day, which includes time for public comment.

ACBSCT SUBCOMMITTEE ON CORD BLOOD

Introduction

Elizabeth Shpall, M.D., Director, Cell Therapy Laboratory and Cord Blood Bank, University of Texas MD Anderson Cancer Center, Houston, TX; Lead Consultant, ACBSCT Subcommittee on Cord Blood

Dr. Shpall explained that the ACBSCT formed the subcommittee to further discuss cord blood, with an emphasis on increasing its utilization in transplantation. HRSA also requested that the subcommittee discuss how to define a "high-quality" cord blood unit (CBU) for the purpose of banking. The subcommittee plans to discuss potential strategies to increase cord blood utilization, provide HRSA feedback on what constitutes high quality, and offer suggestions on potential changes to the NCBI.

The subcommittee met twice in July 2023 to discuss the current state of cord blood banking and utilization. Future meetings may address understanding of patient outcomes and potential changes to NCBI cord blood bank specifications. The subcommittee may also seek to learn more about the experiences of patients seeking a matched donor source.

Current NCBI Contract Specifications

Marcie Finney, M.S., M.B.A., Executive Director, Cleveland Cord Blood Center, Cleveland, OH; ACBSCT Member

The NCBI supports HRSA's mission to improve access to quality health care and services by contracting with cord blood banks to achieve the statutory goal of adding at least 150,000 new, high-quality, genetically diverse CBUs to the NCBI and making them available through the CWBYCTP. Cord blood banks must meet several requirements for participation; for example, they must be public and collect CBUs from a genetically diverse group of donors. They may make some CBUs available for peer-reviewed research (via an FDA-approved research protocol) if the units are not suitable for transplantation. Banks must agree to participate in the CWBYCTP for at least 10 years following federal funding and have contingency plans for transferring and receiving CBUs. Banks must submit NCBI CBU pre-transplant data in compliance with the requirements of the CWBYCTP's Stem Cell Therapeutic Outcomes Database.

In addition, banks must establish a minimum total nucleated cell (TNC) count for NCBI CBUs no higher than the established minimum TNC count for non-contracted public CBUs, by race and ethnicity. They must also have plans to achieve self-sufficiency of CBU collections and operations within 3 years of initiating the contract with NCBI.

Cord Blood Registry Analysis: Current State and Use of Cord Blood Units Listed Through the CWBYCTP

Ericka Narr, Senior Manager, Customer-Ready Products, NMDP, Minneapolis, MN

Ms. Narr summarized results of an analysis to determine the capacity of the cord blood bank industry to meet patient needs for hematopoietic stem cell transplantation (HSCT) and to inform recommendations on enhancing genetic diversity of CBUs, among other topics. Her team analyzed CBU demand from fiscal year (FY) 2018 through FY 2022. Looking only at FY 2022, the analysis found that most CBUs (57%) shipped had TNC counts between 150 and 249×10^7. Ms. Narr pointed out that the distribution of CBUs by TNC remains similar even when assessed over 10 years.

The analysis found that higher TNC counts are favored, regardless of race or ethnicity of the donor or recipient. Lower TNC units have been used for patients of several racial and ethnic groups during the past 5 years. For all racial or ethnic groups other than Pacific Islanders, most CBUs shipped have TNC counts between 150 and 249×10^7.

From a business perspective, Ms. Narr explained, NMDP would recommend banking CBUs with TNC counts greater than 150×10^7, particularly for White, non-Hispanic donors. For non-White donors, NMDP would recommend a TNC greater than 125×10^7. The lower threshold is based on findings that non-Caucasian ethnicity is associated with reductions in hematopoietic measures of collected CBUs and that higher CD34+ and colony-forming unit (CFU) content are associated with Caucasian race. Suggesting the same cell content for units from White and non-White donors would be contrary to diversifying the NCBI, said Ms. Narr. Preselecting donors for TNC is not realistic, as collection volume depends on biological factors and collection technique.

Analysis by CD34+ further demonstrates the preference for larger CBUs. Ultimately, the NMDP recommends a minimum threshold for CD34+ cell content of at least 3×10^6. Enumeration of CD34+ cells can vary by laboratory, which complicates considerations about setting minimum standards for NCBI inclusion. Other guidance recommends a slightly higher threshold.

Ms. Narr said banks could meet demand if the minimum TNC count (90×10^7) were increased. Many banks already require higher criteria for banking units from White donors than for non-White donors. Shipments over the past 5 years show strong interest in CBUs with high TNC counts; distribution is generally similar across most races and ethnicities.

In determining whether increasing collection of CBUs from White, non-Hispanic donors would meet the needs of other races and ethnicities, Ms. Narr said the analysis shows that CBU from White donors are frequently used for non-White patients. Discouraging collection of CBUs from White donors would have a negative impact on the ability to use CBUs from White donors for all patients. Ms. Narr noted that patients receive a CBU from someone of the same race or ethnicity as their own about half of the time. White and Hispanic patients receive grafts from someone of their own race about 65% of the time. Not surprisingly, multiracial patients source units from a variety of races, Ms. Narr concluded.

Cord Blood Utilization—Experience from the MD Anderson Cord Blood Bank

Jeffrey Wilson, Assistant Director, Cord Blood Operations, MD Anderson Cord Blood Bank, Houston, TX

Mr. Wilson and colleagues assessed their own data in terms of NMDP's proposed new TNC and CD34+ thresholds and found that one quarter of MD Anderson's shipments since 2005 would not meet the proposed minimum TNC. Looking at CBUs for transplantation from 2020 to 2022, 14% would not have been banked under the new thresholds, which equates to two transplants per month for the past 2 ½ years. African American recipients would have been particularly affected. Applying the proposed criteria retrospectively to the past year, MD Anderson would have contributed 751 CBUs to the NCBI, rather than the 1,855 CBUs that it contributed under the current threshold. Mr. Wilson said these data suggest the thresholds would affect the availability of units.

Under the new thresholds, banks that have contracts with the NCBI would have to collect four to five times the number of CBUs to deliver the same amount of product, which would dramatically increase operating costs. MD Anderson has 12 collection sites; it would have to triple that number to achieve the higher collection goals. Moreover, NCBI would have to increase the current reimbursement by three to five times per CBU for banks to continue receiving funding at the current level while delivering far fewer CBUs to the NCBI.

Mr. Wilson pointed out that even CBUs with low TNC counts (i.e., small units) save lives, and banks must collect small units to get the large units. Transplant centers select CBUs through NMDP because they represent the best option available for the patient being treated, including small units. Listing smaller CBUs on the registry comes at minimal cost to NMDP. Data analysis shows that MD Anderson has shipped 756 small CBUs for clinical use. Moreover, advances in cellular therapies could mean more clinical uses for small CBUs. Outcome data for use of small CBUs, demonstrated by median time to engraftment, are similar for small and large CBUs. In addition, small CBUs may be ideal for some pediatric patients.

Mr. Wilson emphasized that cord blood banks have different constraints and capabilities that should be taken into account in setting thresholds. These include varying levels of access to a racially or ethnically diverse donor population, different infrastructure and funding, and variations in collection and storage efficiency and capacity. Mr. Wilson concluded that HRSA should continue to contract with each bank based on the bank's ability to meet the needs of the NCBI, recognizing the unique tools and skills of each bank.

Discussion

Summarizing the key messages, Dr. Shpall said 20–30% of CBUs would not be banked under proposed new thresholds, which would be detrimental to the field and the mission of NCBI and HRSA. Collecting larger units under the current procedures would result in throwing away 90% of CBUs collecting from labor units, which would likely be demoralizing to the labor unit personnel. Dr. Shpall said Mr. Wilson made the case for the NCBI to work with individual banks to create unique contracts that take advantage of the bank's capacity. Dr. Shpall said the subcommittee will eventually reach consensus on a recommendation for HRSA.

Nancy L. DiFronzo, Ph.D., asked whether any data describe double cord use for cords with lower TNC counts. Dr. Shpall said there are a lot of data on double cords, and smaller CBUs are

frequently used in double-cord situations. Filippo Milano, M.D., Ph.D., said his team has been focused on expansion with the goal of better matching, using units with lower TNC and CD34+ cell counts, with promising preliminary results. He added that in Seattle, WA, 90% of mismatched transplantations go to White recipients. In his own data on CBUs, 60% are non-White. Dr. Majhail asked Dr. Milano to provide his findings to the ACBSCT at a future meeting.

Juliet Barker, M.B.B.S., cautioned that the issues around CBUs are complicated. The presentations focused on proposed thresholds for TNC and CD34+ cell counts in the context of the inventory, but little consideration has been given to determining the CD34+ dose delivered to the transplant recipient or how to increase the utility of CBUs for transplant centers. Patients are dying waiting for an adult donor, said Ms. Barker. Moreover, many bad CBUs have been banked. Ms. Barker said transplant centers lack guidance and thus select the wrong units, increasing the risk for adverse outcomes. She cited a study published in 2020 by Dr. Milano and colleagues that found that in about 70% of CBU transplants, the transplant center did not follow the minimal acceptable guidelines, which were published in 2020.

Ms. Barker continued that availability of CBUs for people of non-European ancestry is poor, and practitioners are looking at factors other than racial or ethnic match. Among adult patients, transplantation clearly crosses racial boundaries. Ms. Barker did not favor giving banks more money for larger units. For small units, banks can choose what they want to do.

Dr. Shpall pointed out that HRSA has asked the ACBSCT to advise on the definition of a high-quality CBU. HRSA is also concerned with increasing the utilization of CBUs. Expanding utilization must be integrally involved with patient delivery, which Dr. Shpall said the subcommittee should also discuss. She agreed that in addition to dose, the subcommittee should address how to educate transplant centers and promote CBU use.

Ms. Finney said her organization recognized in 2018 the importance of being deliberate about which units are processed, so that the registry reflects the products most valuable for transplant patients. The organization initiated a tiered approach, in which, at a minimum, collectors asked donors about their parents' ethnicity. Ms. Finney said some transplant physicians emphasized the importance of high TNC count, while others said a match is most important, so the tiered approach aims to balance both concerns. The organization instituted a higher TNC threshold for White patients and a lower one for non-White patients. As a result, about half of the units come from White donors, which represents some progress over time in diversifying the inventory.

Ms. Finney added that the lack of innovation in collections is disheartening for staff and donors. She said 60% of units collected are used immediately, which is important for donors to know. At the same time, donors should understand that research is a laudable use of units that could result in helping thousands of people. Ms. Finney called for more discussion about improving collection. She praised NMDP and said it is possible to get high TNC units and good matches.

Ms. Narr said NMDP implemented some mechanisms to help transplant centers select the right unit. For example, while reviewing CBUs but before requesting them, the transplant center must confirm that the CBU is appropriate for the patient's weight. NMDP also reaches out to transplant centers that request CBUs that do not align with current guidelines. Ms. Narr pointed out that one bad experience can turn a transplant center away. Ms. Barker agreed, noting that inappropriate selection is not only dangerous for the patient but can result in a transplant center looking for products elsewhere, creating problems for future patients.

For those new to the ACBSCT, Ms. Grant explained that when HRSA enacted a requirement for cord blood banks to be accredited, it stopped setting specific thresholds for TNC, CD34+, and CFUs. The ACBSCT was established to provide insights on such issues. The criteria are still important, and NCBI banks, transplant centers, and the NMDP likely have the best data on which to base decisions. However, some believe HRSA should clarify the definition of "high-quality," which is why the subcommittee was created.

Dr. Shpall said the subcommittee recognizes that FDA licensure is a rigorous process. It will consider whether HRSA should refine the parameters for CBUs. A bigger issue is increasing use of CBUs to benefit more people and providing education on using CBUs safely. Dr. Majhail asked who should be responsible for establishing guidelines for CBU use. Ms. Barker reiterated that guidelines were already published in 2020. Dr. Shpall noted that the thresholds were created by HRSA and FDA, but the requirements for matching, for example, are harder to define. Clinicians who understand the issues around matching and engraftment must address the questions. Dr. Shpall said it is important to get banks and physicians in the field to reach consensus on how to move forward.

Dr. Majhail said the guidance mentioned by Ms. Barker describes selection of the right units. More guidance may be needed on the parameters to consider, perhaps in the form of a white paper. Ms. Barker said search coordinators at transplant centers are overwhelmed and need help navigating the systems.

Dr. Milano said CIBMTR data confirm that most CBU transplants do not follow published guidelines, which could correlate with poor outcomes. That message should be amplified for the community and HRSA. The data suggest that appropriate units were not selected even when they were available. Dr. Shpall said the subcommittee's next meeting will focus on determining the appropriate units to bank. Once the subcommittee reaches a decision on that issue, it will discuss how to disseminate education on the optimal use of CBUs.

Dr. Majhail suggested that the subcommittee ask Ms. Narr to further describe the distribution of CBUs by age, stem cell expansion technique, and other factors. Dr. Shpall said the subcommittee will look at data coming out. She said the subcommittee could partner with the American Society for Transplantation and Cellular Therapy (ASTCT) on a white paper, which would facilitate dissemination and reach. Dr. Majhail said education should highlight that the issues are more complicated than just meeting threshold numbers.

Dr. Majhail said several comments from the public in the chat focused on the lack of innovation, which could be a topic for discussion at a future meeting. Dr. Shpall said her facility pioneered the use of in utero and ex utero collection, which increases the amount of CBUs and the TNC and CD34+ cell counts. The process has been approved by FDA, and Dr. Shpall offered to share information about the strategy.

INCREASING ACCESS TO BLOOD STEM CELL TRANSPLANTATION

Update on ACCESS Initiative to Address and Sustain Equal Outcomes for All Transplant Recipients

Jeffery Auletta, M.D., Co-Chair, ACCESS Initiative; Senior Vice President, NMDP; Chief Scientific Director, CIBMTR, Minneapolis, MN

Dr. Auletta said that barriers to access to HSCT and cell therapies for ethnically diverse patients translates to inequity and warrants action. The ACCESS Initiative was implemented to reduce barriers to HSCT and cellular therapies with a vision of measuring and advancing progress toward universal access. Its initial areas of focus are awareness, poverty, and racial and ethnic inequity, each of which is addressed by a committee with diverse representation from various stakeholders. The initiative has held two annual workshops to date and presented at the 2023 Tandem Meetings (the combined annual meetings of ASTCT and CIBMTR).

Dr. Auletta summarized progress made by each of the three ACCESS committees over the past year. The Committee on Awareness has created tools for physicians and established relationships with key medical societies. The committee underscores the need for a collective approach to advocate for change as well as the need for updated tools, such as publications that clarify the diseases that can be treated with transplantation. The Committee on Awareness engages a wide range of stakeholders, including those representing the fields of social work, aging, and biobehavioral health, to name a few.

Poverty, whether measured according to the federal poverty level or by real-world indicators, such as lack of insurance, has a significant impact on health. The ACCESS Initiative has called on Medicaid to expand its coverage for diseases that can be treated with transplantation and cellular therapies and to cover the other costs involved, including searching for, acquiring, and paying for transplant products as well as the lodging, food, and transportation costs that beneficiaries face during treatment and follow-up. The initiative is focusing on states with the most restrictive policies and seeks opportunities to educate state Medicaid directors. The Committee on Poverty is evaluating public data to assess how Medicaid policies translate into practice. Kaiser Permanente has granted access to its extensive database so that analysts can compare it with the public data.

The Committee on Racial and Ethnic Inequity includes the NMDP Health Equity team. It has completed an initial survey of transplant centers' needs and interest in engaging in the ACCESS Initiative, as well as a health equity survey and a toolkit for transplant centers. The committee aims to launch a Health Equity in Practice pilot project to increase transplant centers' access to data and resources on health equity so that the centers can better meet the needs of patients. It also hopes to foster a network of transplant centers that can share tools and information.

The ACCESS Initiative's Junior Faculty/Training Initiative is developing tools to train the next generation of health care providers in advocating for equitable care. Dr. Auletta said he believes that every individual has a personal responsibility to work toward positive social change. Working together, individuals can build and sustain change across the entire ecosystem.

Discussion

Dr. Majhail, who co-chairs the ACCESS Initiative Committee on Poverty, praised the multidisciplinary makeup of the group, which has stakeholders from across the spectrum of care.

Ms. Barker pointed out that the definition of low socioeconomic status is strongly affected by how questions are asked, by whom, and the patient's inclination to answer. Dr. Auletta agreed and said the ACCESS Initiative casts a very wide net to identify the underserved population. Ms. Barker said that in asking patients or research subjects about income, her institution had to use surrogate measures to avoid the appearance of discrimination. She said Memorial Sloan-

Kettering Cancer Center is interested in getting involved. Max Grogl, Ph.D., said the Naval Medical Research Center is interested in collaborating.

Dr. Majhail asked how the ACCESS Initiative is funded. Dr. Auletta responded that the effort is volunteer-run. It is seeking financing and in-kind support from industry and private philanthropic organizations. Money from NMDP, ASTCT, Gilead, and Kaiser supports the analysis of Medicaid data.

STATUTORY MANDATE: TIMELY REAUTHORIZATION OF NECESSARY STEM-CELL PROGRAMS LENDS ACCESS TO NEEDED THERAPIES (TRANSPLANT) ACT OF 2021

Robert H. Carter, M.D., Deputy Director, National Institute of Arthritis and Musculoskeletal and Skin Diseases, NIH

Dr. Carter explained that in reauthorizing the CWBYCTP, the TRANSPLANT Act requires periodic review of the state of the science and recommendations on the appropriateness of the inclusion of adult stem cells and birthing tissues as new types of therapies in the CWBYCTP. Scientific reviews must be conducted at least every 2 years, and the first was presented to Congress in May 2023. A report of recommendations to Congress is due by June 30, 2025.

Dr. Carter summarized the purpose of the CWBYCTP and its inclusion criteria. On the basis of the existing criteria, FDA led a review on the state of the science, which incorporated current knowledge of the field and related regulatory actions as well as a literature review. That report found that despite scientific and technologic progress in the field, the present situation with stem cell and birthing tissue products available for clinical use is largely unchanged since the last report in 2019. Therefore, there are no recommendations for additional use of stem cells or birthing tissue products.

Dr. Carter asked the ACBSCT to consider whether the current CWBYCTP inclusion criteria are correct and whether the review of the science was acceptable.

Discussion

Dr. Carter explained that his brief presentation constituted the whole of the report sent to Congress, which was conveyed as an email; he did not know whether a formal written report was created or made available to the public. Ms. Grant said the 2019 report to Congress is available on the HRSA website.

Via chat, a participant said that cord blood and birthing tissues are being used as source material for manufacturing of induced pluripotent stem cells (iPSCs), immune effector cells, and in other emerging technologies. The participant asked whether the NCBI should be allowed to use CBUs to support the development of these emerging technologies. Ms. Grant said that as long as the products are used according to the criteria, then research conducted under FDA-approved protocols is permitted.

Via chat, a participant noted that some products are not directed to a specific, single patient but rather serve multiple patients. Dr. Carter pointed out that the criteria talk about use of a product for a single, designated patient. Ms. Finney said the ACBSCT should discuss potential uses on

the horizon, such as products that may serve more than one patient—for example, through expansion or use of iPSCs. It is possible that CBUs might be combined, expanded, and used in multiple patients, and it is not clear whether the NCBI would permit such use under the current language.

Ms. Grant pointed out that NCBI contractors are not barred from using CBUs in novel ways; rather, the contractors must replace those units. Ms. Finney agreed but said that requirement is counterproductive. Ms. Grant anticipated that innovative research would be conducted under FDA-approved protocols for investigation.

PUBLIC COMMENT

No public comments were provided.

NEW BUSINESS AND DISCUSSION

Dr. Majhail said the ACBSCT had no specific recommendations from this meeting. Ms. Grant noted that past CWBYCTP reports to Congress are posted online.

Action Items

1. The Subcommittee on Cord Blood will continue its discussions and report back to the ACBSCT at a future meeting.
2. The Subcommittee on Drug Shortages, also created in December 2022, will convene and report back to the ACBSCT at a future meeting.

ADJOURNMENT

Dr. Majhail thanked the participants for a robust and enlightening meeting and adjourned the meeting at 4:12 p.m.