

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

U.S. Department of Health and Human Services  
NIH Fishers Lane Conference Center  
Rockville, MD 20852

**Monday, September 15, 2014**

**Welcome and Opening Remarks**

*Edgar Milford, M.D., Chair, ACBSCT*

Edgar Milford, Jr., M.D., ACBSCT Chair, called the meeting to order at 8:23 a.m. and welcomed all council members and other participants to the meeting. He added that this would be the last meeting for several ACBSCT members who were rotating off the council: Claudio Anasetti, M.D.; Richard Champlin, M.D.; Joanne Kurtzberg, M.D.; Richard P. McQuellon, Ph.D., Rebecca Pentz, Ph.D.; Pablo Rubinstein, M.D.; Stephen Sprague; and Susan Stewart. This was also Dr. Milford's last ACBSCT meeting as a member and the council chair.

Dr. Milford asked the heads of ACBSCT workgroups to identify the information that they needed to pass on to the next council. In addition, he pointed out that people who are not members of the council may join council workgroups. Dr. Milford encouraged departing council members to inform the Health Resources and Services Administration (HRSA) if they would like to join a workgroup, which group they would like to join, and what expertise they can offer.

The role of ACBSCT is to advise the Secretary of the Department of Health and Human Services (HHS) through recommendations and to share its expertise with HRSA. Agencies and organizations that also receive the recommendations and advice of the council include the Division of Transplantation, U.S. Navy, National Institutes of Health (NIH), National Marrow Donor Program (NMDP), Center for International Blood and Marrow Transplant Research (CIBMTR), Food and Drug Administration (FDA), Centers for Medicare and Medicaid Services (CMS), and insurers.

**Program Report**

*Shelley Grant, M.H.S.A., Chief, Blood Stem Cell Transplantation Branch, Division of Transplantation, HRSA*

Ms. Grant provided an update on branch activities that have taken place since the May meeting of ACBSCT. The C.W. Bill Young Cell Transplantation Program (Program) and National Cord Blood Inventory (NCBI) are authorized by Congress under the Stem Cell Therapeutic and Research Act of 2005, which Congress reauthorized in 2010.

The goals of the Program are to increase the number of unrelated-donor transplants, conduct recruitment of potential marrow donors, provide patient and donor advocacy services, engage in public and professional education regarding transplantation, and analyze and report on transplant outcome data. The overarching goal is to provide opportunities to help more patients obtain transplants and other therapies using blood stem cells.

The HRSA programs serve a growing number of patients needing unrelated-donor transplantation. As of September 30, 2013, the Program's registry included approximately 11.2 million adult donors. Of these, 27% were members of a racial or ethnic minority group. The programs facilitated 6,283 transplants in FY 2013, a 7.7% increase from FY 2012. The total number of NCBI and non-NCBI cord blood transplants was 1,102 in FY 2013, a 7.4% drop from FY 2012. More than 243,000 NCBI and non-NCBI cord blood units were available through the Program in FY 2013, and 714 NCBI cord blood units were distributed for transplantation that year.

Total funding for the Program was \$22,154,000 and for NCBI was \$11,238,000 in FY 2014. These amounts reflect slight increases since FY 2013. The FY 2015 President's budget calls for similar amounts for both programs.

A challenge for HRSA is balancing the use of Program and NCBI funds to successfully complete all of the functions that Congress has authorized. HRSA is working with the Cord Blood Coordinating Center (CBCC) and cord blood banks to develop strategic priorities to support more robust cord blood initiatives. Through CBCC, HRSA is providing financial support in FY 2015 to select NCBI banks to make cord blood units more rapidly available. HRSA is conducting cord blood bank site visits to better understand the needs of banks, especially given the recent decrease in cord blood use. HRSA did not issue a request for proposals for new NCBI banks in FY 2014, and whether the agency will do so in FY 2015 is not yet known.

HHS issued a notice of public rule making on October 2, 2013, seeking public comment on the proposed change to the definition of "human organ" in the National Organ and Transplant Act of 1984. This change would explicitly incorporate hematopoietic stem cells (HSCs) in peripheral blood in the definition of "bone marrow." HRSA received 533 comments in response to this notice, and next steps are pending.

Since the last ACBSCT meeting, Mary Wakefield, Ph.D., R.N., Administrator of HRSA, received a letter asking if HRSA's information technology systems could provide transplant physicians with any information that a cord blood bank thought was important prior to cord blood unit selection. The answer is yes—HRSA's contractor has a robust computer system that allows cord blood banks to enter relevant information on their cord blood units. The writer also asked whether HRSA has mechanisms to continually evaluate and change, if necessary, the definition of a high-quality cord blood unit. The answer is also yes because ACBSCT performs this function.

Robert Walsh, Director of HRSA's Division of Transplantation, and Patricia Stroup, M.B.A, M.P.A., Senior Advisor of HRSA's Healthcare Systems Bureau and the ACBSCT Executive Secretary, thanked ACBSCT members for taking the time to attend this meeting.

## **Workgroup Report: Advancing Hematopoietic Stem Cell Transplantation for Hemoglobinopathies**

*Naynesh Kamani, M.D., Chair*

Dr. Kamani summarized recent discussions of the Advancing Hematopoietic Stem Cell Transplantation for Hemoglobinopathies Workgroup and two recommendations that the workgroup developed for HHS and HRSA. The workgroup's charges are to (1) identify barriers to transplantation and opportunities to more fully realize its potential for individuals with sickle cell disease and thalassemia and (2) submit for consideration and adoption by ACBSCT recommendations regarding high-priority actions. The reason for the first charge is that even though Hematopoietic Stem Cell Transplantation (HSCT) has been available for almost three decades, blood and stem cell transplantation is underused. Because the underuse is much more substantial in sickle cell disease than in thalassemia, the workgroup focused most of its attention on sickle cell disease.

### Insurance Coverage for HSCT

Since the last ACBSCT meeting in May 2014, the workgroup has discussed insurance coverage for hemoglobinopathies, especially sickle cell disease. The group heard a presentation by Stephanie Farnia, Director of Payor Policy at NMDP, who explained that most children and adults with sickle cell disease have Medicaid coverage. Several third-party insurers cover HSCT for sickle cell disease in their fully funded plans, but about 60% of commercial insurance plans are self-insured, so coverage can vary greatly. Coverage of HSCT for sickle cell disease by state Medicaid programs also varies greatly. The effects of the new health insurance exchanges on sickle cell disease reimbursement are not yet known. Medicare is silent on coverage for sickle cell disease, so decisions are left to contractors who tend to deny coverage of HSCT for sickle cell disease because of its high cost.

NMDP and CIBMTR plan to submit an application for coverage with evidence development (CED) to CMS for HSCT for sickle cell disease. If the request is approved, CMS will provide coverage for patients participating in studies in which patient data collection supplements standard claims data. This CED would be similar to the one that CMS approved for HSCT for myelodysplastic syndrome (MDS) in elderly people. Medicare is collecting data on these procedures to inform its decision about whether to cover this indication.

In 2010, ACBSCT issued the following recommendation:

ACBSCT recommends that the Secretary recognize hematopoietic transplantation for generally accepted indications as a covered benefit for all federal programs for which the Secretary has appropriate responsibility and oversight.

Workgroup members agreed that this recommendation does not serve the interests of people with sickle cell disease because whether sickle cell disease is a "generally accepted indication" is likely to be controversial. Therefore, the workgroup decided to suggest that ACBSCT make the following recommendation to the HHS Secretary that is specific to sickle cell disease:

ACBSCT recommends that the Secretary recognize hematopoietic transplantation for sickle cell disease as a covered benefit for all federal programs for which the Secretary has appropriate responsibility and oversight.

Dr. Champlin seconded the motion, which the council approved.

### Increasing HSCT Awareness

The workgroup also discussed ways to increase health-care provider and patient/parent awareness of HSCT for sickle cell disease. Raising awareness will lead to increased referrals for HSCT for eligible patients with sickle cell disease. The workgroup is considering a perspectives article or white paper presenting the evidence in the literature on the role of HSCT in sickle cell disease. Other proposed activities are education sessions at health-care provider meetings and conferences of patient advocacy organizations and a call for prompt publication of findings from clinical trials and CIBMTR data.

### Evidence on HSCT in Sickle Cell Disease

The National Heart, Lung, and Blood Institute (NHLBI) recently published guidelines for sickle cell disease management. These guidelines mention HSCT as a therapeutic option only briefly.

Current clinical trials for HSCT in sickle cell disease include:

- Evaluating the Safety and Effectiveness of Bone Marrow Transplants in Children With Sickle Cell Disease (SCURT): Pediatric Phase II trial on mismatched, unrelated HSCT
- Bone Marrow Transplantation in Young Adults With Severe Sickle Cell Disease (STRIDE): Reduced-toxicity HSCT for young adults with sickle cell disease
  - An R01 application will be submitted for an expanded trial in 60 people aged 16-40 years with sickle cell disease to compare matched and mismatched unrelated-donor HSCT with standard of care.
- Nonmyeloablative allogeneic HSCT trial in 30 adults with sickle cell disease (*JAMA* 2014;312:48-56)
- Nonmyeloablative haploidentical HSCT trial in 17 adults with sickle cell disease (*Blood* 2012;120 4285-4291)

### Number of Patients Undergoing HSCT for Sickle Cell Disease (SCD)

The numbers of patients with sickle cell disease undergoing a first allogeneic HSCT that was reported to CIBMTR have risen steadily in the past two decades, especially in the last few years. Although this increase is encouraging, HSCT is still vastly underused for sickle cell disease.

The CIBMTR data show that approximately 400 to 500 patients with sickle cell disease underwent HSCT in the last few years. Data on these patients need to be analyzed, which is only possible if transplant centers provide more detailed information to CIBMTR. Transplant centers are required only to provide very basic data, and they would need additional resources to collect disease-specific research-level data. The workgroup therefore offered the following recommendation for HRSA:

Provide financial support to the CIBMTR to enable the prospective collection of sickle cell disease-specific research-level data for patients undergoing hematopoietic cell

transplantation for SCD at transplant centers that elect to be CIBMTR research centers contingent upon Office of Management and Budget (OMB) approval.

## **Discussion**

### Recommendation on Insurance Coverage

The ACBSCT discussed the workgroup's recommendation regarding insurance coverage for HSCT. Joanne Kurtzberg, M.D., pointed out that this recommendation addresses a major unmet need.

Dr. Milford requested clarification on the process that CMS would use to implement the recommendation. Dr. Kamani replied that the HHS Secretary oversees CMS. Furthermore, implementation of the recommendation by CMS would influence other federal programs over which the Secretary has authority.

Dr. Schriber, asked whether a piecemeal approach is preferable to recommending Medicare coverage for many diseases that would benefit from HSCT and are not addressed in Medicare policies. Dr. Kamani agreed that other diseases would benefit from CMS coverage. The workgroup's concern, however, was that the council's previous recommendation referred to "generally accepted conditions," a term that might not apply to sickle cell disease. Experts in HSCT for sickle cell disease know that transplantation is beneficial to many of these patients, but the published guidelines do not call for this treatment in this setting.

Dr. Price asked about data on the numbers of patients who are eligible for transplantation but do not receive one because of lack of insurance. Dr. Kamani said that insurance is only one of many barriers to HSCT in sickle cell disease. For this reason, it is not possible to quantify the need.

Dr. Campbell commented that families are now asking about HSCT for sickle cell disease, and they will increasingly request that their insurance plans cover the procedure.

Dr. Schriber asked about the timeframe for implementing a CED for sickle cell disease. Dr. Kamani said that the process is lengthy.

Dr. Schriber pointed out that the CED for MDS led to a substantial increase in the numbers of patients with MDS undergoing HSCT. Ms. Stayn asked whether the council should endorse the 2010 recommendation.

Dr. Milford suggested sending all ACBSCT recommendations to the new HHS Secretary to ensure that she is aware of the history of the council's latest recommendation. Mr. Walsh explained that the council's recommendations are made to the Office of the Secretary and not the individual Secretary. Officially, council recommendations continue to be acted on when a new Secretary takes office. However, there is no harm in restating them for the new Secretary.

### **Action:**

ACBSCT will send a list of its previous recommendations to the HHS Secretary.

Dr. Schriber asked for a list of all council recommendations and their results for distribution to ACBSCT members. Dr. Milford said that such a list has been prepared and should be revisited.

**Action:**

HRSA will revise the list of all council recommendations and their results and distribute this list to ACBSCT members.

Ms. Stayn asked about the effect of the 2010 recommendation on CMS coverage for generally accepted conditions other than MDS. Dr. Kamani clarified that whether the CMS CED for MDS resulted from the 2010 council recommendation is not clear. NMDP and others also requested a CED for HSCT at the same time as ACBSCT.

Dr. Walters expressed concern that the latest sickle cell disease guidelines do not strongly endorse HSCT for this indication. Payors might view HSCT as experimental for sickle cell disease, which could affect their coverage decisions. This misinterpretation needs to be addressed. Dr. Champlin explained that the benefits of HSCT as a curative treatment for hemoglobinopathies have been established, and current research is focusing on how best to use HSCT for these diseases. This message needs to be communicated to insurance companies.

Dr. DiFronzo said that NHLBI is revising its website, which will include information on sickle cell disease. She suggested that the council talk to Keith Hoots, M.D., Director, Division of Blood Diseases and Resources at NHLBI, to ensure that the website conveys the appropriate information on HSCT for sickle cell disease.

Recommendation on CIBMTR Data

Ms. Grant explained that HRSA's contract with CIBMTR does not include funding to collect data. This does not mean that HRSA could not provide funding for this purpose. However, if HRSA allocates funding to data collection, it would need to use funds currently used to support another activity. Dr. Mary Horowitz, Chief Scientific Director at CIBMTR, added that transplant centers receive no reimbursement for providing the data mandated by the Stem Cell Therapeutic and Research Reauthorization Act. Requiring CIBMTR to use some of its funds to support additional data collection will not be helpful unless CIBMTR's overall funding increases.

Dr. Kurtzberg wondered whether HRSA could redirect its funding without legislative direction. She noted that the Stem Cell Therapeutic and Research Act is due for reauthorization in 2015, and it might be possible to add new priorities to the legislation at that time.

Ms. Grant reported that contractors submit approximately 60 percent of research-level data for sickle cell disease. She also explained that any plans to collect outcomes data must be reviewed and approved by the Office of Management and Budget (OMB), and the approval process can take up to a year. It is important to avoid stopping the current data collection process while waiting to complete an extensive review process. In response to a question from Dr. Milford

about forms currently in use, Ms. Grant explained that none of the existing forms that have OMB clearance are appropriate for collecting outcomes data on patients with sickle cell disease.

Dr. Douglas Rizzo, Project Director, Stem Cell Therapeutic Outcomes Database, explained that OMB has approved the forms that are used by the database. Any changes to the forms must undergo OMB approval. Other mechanisms, such as NIH funding, might offer more suitable resources for collecting research-level data on patients with sickle cell disease.

Several ACBSCT members agreed to revise the workgroup's reimbursement recommendation for presentation later in the meeting to incorporate some of the points made during this discussion.

### Revised Reimbursement Recommendation

Dr. Kamani subsequently presented the following version of the recommendation:

ACBSCT recommends that the Secretary direct HRSA and other HHS agencies to collaborate with the CIBMTR to review research-level data collection on allotransplants performed for sickle cell disease and consider appropriate reimbursement for research data collection. This review should include sickle-cell-disease-specific data elements collected, the completeness of data collection, and mechanisms for reimbursement.

Dr. Champlin pointed out that the earlier version of the recommendation encouraged the collection of research-level data, but the newer version did not. Dr. Kamani explained that CIBMTR already collects research-level data on 60% of transplants for sickle cell disease, but Dr. Champlin suggested that the recommendation aim for 100%. Dr. Kamani noted that the submission of these data is voluntary. Council members suggested that Dr. Kamani revise the recommendation slightly.

Dr. Kamani then presented the following revised recommendation:

ACBSCT recommends that the Secretary direct HRSA and other HHS agencies to collaborate with the CIBMTR to review research-level data collection on allotransplants performed for sickle cell disease and consider appropriate reimbursement to optimize research data collection. This review should include sickle-cell-disease-specific data elements collected, the completeness of data collection, and mechanisms for reimbursement.

Dr. Pentz seconded the motion, which carried.

### **Office of Human Research Protections: Overview**

*Irene Stith-Coleman, Ph.D., Director, Division of Policy and Assurances*

Dr. Stith-Coleman described the mission and activities of the Office of Human Research Protections (OHRP) in the Office of the Assistant Secretary for Health at HHS. The OHRP mission is to provide leadership in the protection of the rights, welfare, and wellbeing of subjects

involved in research conducted or supported by HHS in accordance with the HHS protection of human subjects regulations in 45 CFR part 46. The office accomplishes its mission by providing clarification and guidance, developing educational programs and materials, and maintaining regulatory oversight.

OHRP has four components:

- Office of the Director: Jerry Menikoff, M.D., J.D., Director of OHRP, serves as the Executive Secretary of the Secretary's Advisory Committee on Human Research, and the office provides training on ethical human subjects protections to institutions involved in international research.
- Division of Compliance Oversight: This office evaluates written substantive indications of noncompliance with HHS protection of human subjects' regulations, determines regulatory actions needed to protect human subjects, and conducts site evaluations of research institutions.
- Division of Education and Development: This office conducts national and regional conferences, provides guidance to individuals and institutions conducting HHS-supported human subjects research, develops and distributes resource material to improve protections for human subjects, and helps institutions assess and improve their human research protection programs.
- Division of Policy and Assurances: This office prepares and disseminates policies, guidance documents, and interpretations of requirements for human subjects protections; coordinates appropriate HHS regulations, policies, and procedures within HHS and with other federal agencies; administers assurances of compliance; and implements the institutional review boards (IRBs) registration process.

## **Discussion**

Ms. Grant asked whether the OHRP national and regional conferences are open to the public. Dr. Stith-Coleman explained that institutions submit requests to OHRP to co-host conferences with OHRP. These conferences are not typically open to the public.

## **Barriers to HSCT Access**

*Richard Champlin, M.D., Chair, Access to Transplantation Workgroup*

Dr. Champlin discussed the current uses of HSCT, barriers to its use, and ways to overcome these barriers.

## Trends in HSCT Use

HSCT is an effective treatment for a broad range of hematologic, immune, metabolic, and neoplastic diseases. According to CIBMTR data, the number of autologous and allogeneic transplants has risen steadily since the late 1980s. The most common indications for allogeneic HSCT in the United States are acute myelogenous leukemia (AML), acute lymphocytic leukemia, chronic lymphocytic leukemia, lymphoma, and MDS.

HSCT is high-risk, high-reward treatment. Approximately 10 to 30 percent of patients who undergo HSCT die from a treatment-related cause within the next year or two. But HSCT provides the greatest chance of long-term survival and cure for many patients.

### HSCT in Older Patients

Only about 15 percent of patients younger than 70 with a hematologic malignancy that is treatable by HSCT undergo this procedure. A barrier to HSCT is that older patients and patients with certain comorbidities or disease states are not considered eligible for HSCT. Furthermore, HLA-matched donors are not always available, physicians do not refer all eligible patients for the procedure, and the procedure is expensive and requires a lengthy stay near a transplant center.

Hematologic malignancies are most common in older people. Although some older patients are unable to tolerate HSCT due to their physical condition, researchers have made progress in treating older patients successfully using reduced-intensity regimens that are less toxic and more tolerable. In patients in their 60s and 70s, reduced-intensity HSCT improves disease-free survival compared to standard chemotherapy.

### Insurance Coverage for HSCT

Lack of medical insurance coverage is a major barrier to HSCT. NMDP has developed a list of provisions that insurance plans covering HSCT should include.

The Patient Protection and Affordable Care Act (ACA) of 2010 requires insurers to cover several categories of care. Although these categories do not mention HSCT or other types of transplantation, they do cover aspects of HSCT. The health insurance exchanges established under the ACA have enrolled millions of people, but whether people enrolled in lower-cost plans will have access to HSCT at centers of excellence is not clear.

CMS programs now cover HSCT for MDS under a CED. A large study is evaluating the outcomes of HSCT in this setting. Transplantation also has a clearly beneficial role in lymphoma and myeloproliferative diseases, but the procedure is not covered for these diseases.

Clinical trials offer the best care available. They are developed by experts, undergo rigorous scientific review, and are actively monitored. Many insurers do not cover participation in clinical trials, even now that ACA requires them to do so.

### How to Overcome Barriers to HSCT

Referring physicians need to become familiar with the indications for HSCT. Many have misperceptions about the toxicity and outcomes of the procedure, and they do not keep up with the rapid developments in the field. Furthermore, because of financial disincentives, patients are often referred to HSCT too late to have an optimal outcome. Physicians must be encouraged to make appropriate referrals, and the resources (including facilities and staffing) required for HSCT must be expanded. Reimbursement must induce centers to invest in HSCT development.

Patients and families need education on the benefits and risks of HSCT. They need financial support to cover the costs of travel to a transplant center and of staying near a transplant center for several months. Caregivers need emotional and financial support as well.

HSCT results are best when an HLA-matched sibling is the donor. But results from umbilical cord blood and haploidentical transplants are almost as good as from matched unrelated or sibling donors. Thus, almost every patient now has a donor. The chance of finding a suitable matched donor is highest, at 75 percent, for white European patients. The likelihood is much lower for individuals from other ethnic and racial groups.

Another need is to help patients find a good doctor and transplant center. CIBMTR collects data on survival rates by transplant center, and these data are publicly available.

## **Discussion**

Dr. Milford asked what messages this workgroup would like to convey to the next council. Dr. Champlin replied that the next council should monitor enforcement of ACA requirements, particularly those pertaining to coverage of clinical trial participation.

Dr. Schriber asked whether the council should issue a recommendation regarding CMS coverage for lymphoma and other diseases in which the benefits of allogeneic and autologous HSCT have been clearly established. Dr. Champlin said that the situation for lymphoma is very complicated. Some registry studies have shown, for example, that allogeneic transplantation is not better than autologous transplantation for lymphoma.

## **The ACA and HSCT Concerns and Strategies**

*Michael Boo, J.D., Chief Strategy Officer, NMDP*

NMDP recently created resources that address reimbursement for HSCT, including CMS donor search cost memos, the Medicare Billing Toolkit, webinars, monthly newsletters, and the Payor Resource Center. NMDP formed the Advisory Group on Financial Barriers to Transplant, which focuses on barriers related to health insurance coverage or benefits. This advisory group includes physicians, administrators, and representatives of payers and transplant networks. The group produced a list of recommended HSCT benefits for payors.

Access to HSCT will probably increase because of ACA and other health-care reform initiatives. A new concern is the recent federal district court ruling that premiums for policies purchased through a federally sponsored health insurance exchange are not eligible for federal subsidies. The Department of Justice has appealed this ruling.

NMDP continues to monitor the impact of ACA on HSCT. The program has asked transplant centers to share stories of people who have had difficulty obtaining coverage or whose request for coverage was denied because they did not receive their transplant at an approved center. NMDP will bring these stories to HHS to show the importance of complete coverage for HSCT. NMCD will also make Congress aware of the access issues within the exchanges. In particular, NMDP plans to determine whether ACA's definition of "essential health benefits" covers all of

the elements in the NMDP list of recommended HSCT benefits for payors. Other issues to monitor are limitations on coverage reimbursement by element (e.g., cancer care or pharmaceuticals), use of external review appeals processes, qualifications of appeals' process reviewers, and coverage of clinical trials by payers as required in ACA. NMDP is designing studies that demonstrate to policy makers and insurers that covering this procedure is money well spent.

The number of transplants among adults older than 60 that are covered by Medicare and Medicaid is increasing, and the proportion covered by commercial plans is dropping. The Medicare reimbursement rates for HSCT are low. NMDP is seeking separate reasonable cost-based reimbursement for search and procurement of HSCs and complex ambulatory care payment status for outpatient HSCT. NMDP is also working with the American Society for Bone Marrow Transplantation and the American Society of Hematology on physician reimbursement issues.

Medicare covers allogeneic transplant for leukemia, severe combined immunodeficiency, Wiskott-Aldrich syndrome, and MDS (through the CED). Medicare explicitly does not cover allogeneic transplant for multiple myeloma or specify whether it covers lymphomas, myeloproliferative diseases, sickle cell disease, or other diseases. If CMS does not explicitly mention a condition, local fiscal intermediaries decide whether to cover that indication. These intermediaries do not provide preapproval for transplant. Because HSCT is so costly, transplant centers are often unwilling to perform a transplant knowing that they might not be reimbursed afterwards. NMDP has recommended that CMS address these indications through a coverage decision.

Until 2010, Medicare-eligible patients received very few transplants. After CMS approved the CED, the number of related and unrelated allogeneic transplants in those older than 65 increased significantly. This experience shows that a positive indication decision immediately increases access for many patients who would otherwise not undergo the procedure.

Obtaining approval for a new CED takes a long time. NMDP is therefore pursuing an "umbrella" CED that provides coverage for HSCT for several indications. However, CMS has indicated that NMDP will still need to show that HSCT is effective in each therapy, at least in people younger than 65 who are covered by the Medicare disability provisions.

## **Discussion**

Dr. Milford commented that a representative from CMS told ACBSCT a few years ago that any party may apply to CMS for a coverage decision. If CMS denies the request, the agency will not provide coverage. Mr. Boo agreed that asking for a coverage decision is risky for this reason, noting that CMS denied coverage for multiple myeloma. This is a reason why NMDP is pursuing a CED; if CMS denies the request, the agency could still cover HSCT for the relevant indications at a later time.

Dr. Milford asked about the results of the NMDP survey on transplant needs in the future. Mr. Boo replied that the NMDP capacity initiative surveyed the network to learn about capacity

in terms of facilities and professionals. The results showed that the current system does not have the capacity to handle all potential transplants. NMDP is therefore working with professional societies to increase training for health professionals in transplantation.

Ms. Stayn asked whether patients could undergo expedited review in clinical trials. Mr. Boo said that data on people younger than 65 must show that the procedure is beneficial before a request for coverage in older patients will be considered, and such data are limited. So it is not possible to request coverage for those older than 65. NMDP tried to avoid this issue by requesting an umbrella CED based on therapy rather than indication, but this effort was unsuccessful. NMDP now needs to determine how much data are enough to support an indication.

Dr. Schriber noted that the shift toward more coverage by Medicare and Medicaid for HSCT for eligible populations and less coverage by commercial plans might reduce the ability of transplant centers to continue expanding because their profit margins could decline.

### **Workgroup Report: Realizing the Potential of Cord Blood**

*Thomas Price, M.D., Chair*

Dr. Price provided an update on the recent activities of the Workgroup on Realizing the Potential of Cord Blood, which recently merged with the Scientific Factors that Make a Unit High Quality workgroup. The merged workgroup has 10 members and has had three conference calls.

Dr. Price provided an update on each of the workgroup's charges:

- Continue to evaluate the characteristics of a quality cord blood unit: The workgroup is collecting information from NMDP and CIBMTR.
- Reconsider the HRSA total nucleated cell (TNC) threshold for reimbursement: Transplant physicians typically order units with a high TNC count, and processing low-TNC units is not cost effective. These findings support raising the TNC threshold to promote the financial health of cord blood banks. However, TNC counts in cord blood from African Americans tend to be lower than in Caucasians, and a higher TNC threshold could adversely affect the ability of minority patients to find a suitable unit.
- Identify gaps and opportunities in clinical research and technology in regard to use of cord blood in cellular therapy and regenerative medicine: The workgroup has formed a subcommittee, chaired by Colleen Delaney, M.D., M.Sc., to address this issue.
- Evaluate collection models that would simplify and streamline consenting and screening: The workgroup is considering whether Institutional Review Board (IRB) review is required to collect and bank cord blood units. Transplant recipients are treated as research participants but cord blood unit donors are not, and different institutions have different practices with respect to IRB reviews for cord blood units. The workgroup will work with OHRP and NMDP to prepare a presentation on this issue at the next ACBSCT meeting.

- Evaluate the impact of declining use of cord blood on cord bank finances: Cord blood use has dropped in recent years. The workgroup is awaiting an NMDP financial analysis of member banks.

**Action:**

The Workgroup on Realizing the Potential of Cord Blood will work with OHRP and NMDP to prepare a presentation on this issue at the next ACBSCT meeting.

**Discussion**

Dr. Kurtzberg calculated that approximately five times more units would need to be collected from African Americans to obtain the same proportion of banked units as for Caucasians if the TNC threshold rises. People from African American and mixed racial and ethnic backgrounds rely on cord blood more than Caucasians because these populations have difficulty finding matched units from other sources.

Robert Hartzman, M.D., commented that transplant physicians always want to find the largest unit that will meet their patient's needs. If the TNC threshold rises, physicians might ask for even larger units. Instead of changing the TNC threshold, the focus should be on making transplants with cord blood units more successful. Dr. Walters asked whether the quality of cord blood units can be established in any way other than their TNC counts.

Dr. Price pointed out that whether each center selects units based on TNC count or another basis is not known. However, patient survival is best with higher cell doses. Dr. Kurtzberg reported that the data on the effects of high cell dose are mixed. Most data indicate that increasing cell dose beyond a certain threshold conveys no additional benefit.

Dr. Schriber asked whether data are available that define the threshold by ethnicity.

Dr. Kurtzberg said that the threshold for cord blood is the same in different ethnicities.

Dr. Confer, of NMDP and CIBMTR, said that collecting cord blood units for banking purposes only does not require IRB approval. Some units that are not used for transplantation might be suitable for research if they are deidentified. When an institution collects cord blood units, it might require IRB approval if at least some of the units will be used in research. NMDP will work with the workgroup and OHRP to clarify this issue.

**Likelihoods of HLA Matches for HSC Grafts in the U.S. Unrelated Donor Registry**

*Mary Eapen, M.B.B.S., M.S., Professor, Medical College of Wisconsin; Senior Scientific Director—Research, CIBMTR*

Dr. Eapen presented data on the likelihood of finding an HLA-matched or HLA-unmatched unrelated HSC donor in the U.S. Unrelated Donor Registry for adults and children.

The gold-standard donor for HSCT is a matched sibling. When a matched sibling donor is not available, options include an HLA-mismatched donor, a haploidentical related donor (parent, sibling, or child), or a cord blood unit.

NMDP maintains the U.S. Unrelated Donor Registry, which lists more than 10.5 million adult volunteers and has 200,000 unrelated cord blood units.

The highest priority when choosing HSCs from an unrelated donor is matching all 8 HLA antigens. Units match 7 of the 8 HLA loci reduce the patient's chance of survival by 8 to 10 percent but this option is considered clinically acceptable for patients who would otherwise die of blood cancer.

For cord blood units, up to 2 of 6 antigen mismatches are tolerated. Several studies have shown that in spite of these lower standards, survival rates are similar in patients who have undergone HSCT from matched and mismatched unrelated cord blood donors.

Not everyone who might benefit from HSCT has a suitably matched unrelated donor in the U.S. Registry because HLA gene polymorphisms are common and allelic variation is population specific. An analysis of registry data at the end of 2012 showed that Caucasians have a 75 percent likelihood of finding an 8/8 matched, unrelated donor. But the likelihood of finding an 8/8 matched unrelated donor is much lower (30 to 50 percent in other ethnic groups and is particularly low in those of African descent (16 to 19 percent). These investigators predict that by 2017, when the number of donors will rise by 5.5 million, the chances of finding an unrelated 8/8 matched donor will increase by only 4 to 7 percent.

Patients are most likely to find an unrelated donor from their racial and ethnic group. Most people in the U.S. Registry are Caucasian, and most donors chosen for Caucasian patients are Caucasian. The overall likelihood of finding a matched donor from one's own ethnicity is about 35 percent for patients from other ethnic backgrounds.

If an 8/8 matched unrelated donor is not available, the next choice might be an unrelated cord blood unit. In children, 75 percent of Caucasian patients can find an 8/8 matched unrelated donor, and most other patients can find a 5/6 matching unrelated cord blood unit. In adults, most cord blood units are a 4/6 match.

Another strategy when an 8/8 matched unrelated donor is not available is to find a 7/8 matched unrelated donor. The next choice is then a cord blood unit. With this strategy, more than 90 percent of people of any race can find a donor. Waiting an additional two months to find a matched donor is unsuccessful in more than 95 percent of cases, so using an unmatched donor might be a better strategy.

## **Licensure Challenge: Cord Blood Banks that Are Not Licensed**

### **Cleveland Cord Blood Center Biologics License Application**

*Mary Laughlin, M.D., Medical Director, Cleveland Cord Blood Center*

Dr. Laughlin described the Cleveland Cord Blood Center's (CCBC's) preparation of a biologics license application (BLA) to the FDA. This nonprofit blood bank was established in 2007 with generous philanthropic funding. The center has 5,870 cord blood units available for searching.

It has distributed 5,760 units for research and shipped more than 250 units to transplant centers in the United States and 13 other countries.

CCBC held its first pre-BLA meeting with the FDA in 2010 and learned that the bank was not ready to submit a successful BLA. Since then, CCBC has been actively engaged in preparing for its BLA submission in April 2015, which the bank expects to be successful.

CCBC hired a consulting group to complete a good tissue practice/good manufacturing practice gap analysis audit and provide regulatory advice. The consultants have now reviewed the bank's facilities and chemistry, manufacturing, and controls documentation required for the BLA to assess CCBC's compliance with submission requirements.

To comply with the FDA requirements, CCBC has purchased new equipment that provides adequate backup for every function in the processing facility, redesigned its clean room to accommodate critical aspects of aseptic processing, added a new receiving area and accessioning work area, and removed all non-essential stations from the processing facility. CCBC has also made leasehold and security system improvements to expand its offices to accommodate these changes and moved its administrative functions into a separate area.

CCBC has hired three new staff members (processing facility director, quality control technician, and two processing facility technicians) to address BLA requirements at an annual cost of almost \$300,000. The cost of consulting services to date is \$130,000. CCBC purchased document management, error management, and laboratory information system software. The cost of this software, its implementation, and associated training was almost \$400,000. The total capital cost of the modifications to meet the FDA requirements was more than \$900,000. CCBC covered some of this amount from a state grant.

CCBC estimates that it will bank 1,350 units and distribute 75 units a year. Offsetting the costs of preparing the BLA and meeting FDA's ongoing requirements would cost an additional \$7,500 per unit.

Preparation of the CCBC BLA has resulted in a personnel and financial burden for which funding is not currently available. The bank has spent almost \$1.3 million on capital improvements, consultants, and other costs to prepare for the BLA. The bank expects to incur \$600,000 in ongoing costs each year, not including equipment depreciation. Licensure will not improve the quality of CCBC's cord blood units. Dr. Laughlin concluded that this business model might not be sustainable.

### Discussion

Dr. Champlin asked whether CCBC will charge more per cord blood unit to cover its BLA-related expenses. Dr. Laughlin replied that charging more would not be wise. CCBC has committed and sustained philanthropic funding and relies on its unit distributions to recoup its operating costs. If the bank's distributions remain the same or increase slightly, it will remain revenue neutral. However, the BLA process is associated with risks from a business perspective.

Dr. Champlin reported that many programs in Asia are using haploidentical units because of the high cost of cord blood units. Dr. Laughlin said that although data on haploidentical transplant are promising, it is too early to know whether event-free survival rates are the same with haploidentical and cord blood transplantation.

Dr. Milford asked about CCBC breakeven revenue per unit. Dr. Laughlin explained that the bank currently charges \$35,000 per unit. NMDP suggested that the bank reduce its fee, but the bank cannot do so with its current distribution rate. The bank will need to increase its distribution to a level that yields \$600,000 or rely on philanthropic donors.

**Bergen Community Regional Blood Center, Inc.**

*Dennis Todd, Ph.D., Chief Executive Officer*

Dr. Todd reported on the status of cord blood collection by the Bergen Community Regional Blood Center (known as “Bergen”) and its BLA preparation. Bergen is a nonprofit corporation that collects and processes blood and platelets and distributes units in northern New Jersey and Southern New York. Bergen also operates the New Jersey Cord Blood Bank, Elie Katz Umbilical Cord Blood Program, HLA Registry, and an NMDP-affiliated apheresis center. In 2013, Bergen distributed 100,000 products, making it a small to moderate-sized blood center.

Bergen charges \$35,000 for each cord blood unit and donates units for uncompensated care patients. Bergen does not charge New Jersey researchers for units used in qualified laboratory studies. The bank receives support from NMDP, NCBI, and some private donors. The bank received a \$150,000 grant from the state a few years ago but has not received state contributions recently.

The number of blood transfusions has decreased by 30percent in the past 5 years. State and federal regulations are increasing, and blood banks face more pricing pressure. Support for Bergen’s cord blood program has declined recently and is likely to continue to drop.

As of August 2014, Bergen has approximately 6,100 cord blood units, of which 1,800 are NCBI qualified. So far, Bergen has shipped 275 units for transplant. Bergen sells non-qualified units to pharmaceutical companies for research. Less than 10 percent of Bergen’s cord blood units qualify for banking, and 25 percent of the inventory has a TNC count lower than 900 million cells.

Bergen operates five collection sites in hospitals that serve large minority groups. To conserve or reduce expenses, Bergen has closed four other collection sites.

To prepare its BLA, Bergen has hired consultants, built a clean room, revalidated its procedures, and developed an online training program for collectors. Bergen plans to file its BLA at the end of 2014 or in the first quarter of 2015.

Dr. Todd concluded that without the support of its stem cell contracting program, the New Jersey Cord Blood Bank would not be self-sufficient. Bergen’s public banking program could not survive without support from HRSA and an NCBI contract.

## Discussion

Adrian Gee, Ph.D., asked about the cost of preparing a successful BLA. Dr. Todd replied that Bergen has spent \$500,000 to date on BLA-related activities and it will spend more before its submission. He added that Bergen could probably break even by distributing approximately 60 to 70 units a year.

Dr. Kamani asked whether Bergen's private cord blood bank subsidizes its public bank. Dr. Todd said that the private bank does support the public bank. Bergen established its private cord blood banking program in response to a state request. This program now provides contracting services to other private banks throughout the United States and in other countries, generating approximately \$1.2 million a year.

Dr. Milford asked about the likelihood that Bergen will reach a steady state by distributing 60 or more cord blood units a year. Dr. Todd said that Bergen shipped about 20 units this year, and the number is unlikely to grow. Without major changes in the field, Bergen will not achieve a steady state in the near future.

### **J.P. McCarthy Cord Blood Stem Cell Bank**

*Voravit Ratanatharathorn, M.D., J.P., Director*

Dr. Ratanatharathorn described the J.P. McCarthy Cord Blood Stem Cell Bank, which has about 2,200 cord blood units in its inventory. The bank distributed 19 units last year. Because the bank receives HRSA funding, its breakeven point is approximately 20 units a year.

A major concern is the drop in the number of cord blood units shipped in recent years; this number declined even more drastically this year. To date, the bank has shipped only 11 units this year and does not expect to reach 20 units as it did last year. Therefore, the bank will operate at a loss. The reason the bank can be sustained is its low operational cost. The bank uses a shared facility with a stem cell processing laboratory for clinical transplantation and has a production facility for immunotherapy. All technicians work in all of the facilities.

Dr. Ratanatharathorn expressed concern about the poor reimbursement rates for transplants. Because of the low reimbursement rates, the McCarthy Bank cannot afford to proceed with a BLA.

## Discussion

### *FDA Regulations*

Ms. Stayn asked for an FDA representative to comment on the high costs of preparing a BLA by cord blood banks and ways to alleviate this cost. Dr. Ratanatharathorn added that many small cord blood banks cannot afford to prepare a BLA. As a result, many banks will continue to distribute non-licensed cord blood units but will have stop collecting cord blood. Ellen Lazarus, M.D., explained that the issues raised are not directly related to FDA regulations.

Dr. Lazarus pointed out that the FDA's dockets of administrative proceedings and rule making are open to the public. The FDA would like to know of data showing that particular practices or standards in these guidance documents are not valuable. The agency relies on scientific data, including professional standards, to develop its standards. The cord blood banking community should inform the agency of any measures that are outdated and should be dropped.

Dr. Champlin commented that undoing regulations is difficult. The council should identify regulations that could be scaled back to make the cord blood banking process more cost effective. Dr. Kurtzberg suggested separating collection from processing and making collection the responsibility of hospitals.

Dr. McCullough suggested that the council identify the FDA requirements that are unnecessary to ensure safety and that make cord blood banking more costly. However, FDA will need data to justify changing its policies.

Dr. Laughlin argued that the BLA process restricts cord blood banks to a single procedure and inhibits innovation.

#### *Effects of Licensure*

Dr. Kurtzberg stated that many processes involved in obtaining a license increase costs without improving quality. One reason is that cord blood banks are asked to comply with drug regulations that are not relevant to protecting the quality of cord blood cells. This issue applies to many other cell products. For example, the BLA requires shorter storage times than are necessary to successfully transplant cord blood units. Changing these regulations would require legislation.

Dr. Rubinstein agreed with Dr. Kurtzberg. Preparing a BLA is difficult and requires a significant investment of personnel and money. However, he believes that licensure is useful. For example, the requirement to establish batch records resulted in the creation of electronic batch records at the New York Blood Center. Physicians now use this system to obtain details on the center's almost 60,000 units. Many other requirements for licensing, such as environmental controls, have also benefited cord blood banks. However, the requirements have not decreased the number of contaminated units.

Dr. Rubinstein added that obtaining a license in the drug industry is advantageous, especially in a financial sense. However, obtaining a license provides no advantages to cord blood banks. Furthermore, the leaders of cord blood banks need to determine how to function in the current environment. The future of the field lies in synergizing the ability of all U.S. blood centers and finding ways to lower costs and raise quality. This topic is an important area for the new ACBSCT members to discuss.

Dr. Todd explained that Bergen's cord blood program has always complied with blood banking standards. He added that today's blood centers could not pass the FDA's inspection requirements for cord blood banks.

### *Costs of Cord Blood Banking*

Dr. Champlin commented that the cost of cord blood units is already high. If these costs increase to comply with regulatory requirements, the competitive place of cord blood with respect to other cell sources will be further compromised. The leaders of the cord blood unit at Dr. Champlin's institution believe that for the bank to be competitive, the cost of a unit of cord blood must be the same as the cost of a bone marrow or peripheral blood unit.

Dr. Kurtzberg said that cord blood banks are in a no-win position. They face pressure to cut their costs to remain competitive in the transplant business, but their costs are increasing because of licensure requirements.

Dr. Milford summarized the issues that the council had discussed: whether the existing standards are appropriate for protecting the public's health and whether the costs of cord blood banking will reduce the availability of this resource for health. The latter is more important based on the discussion. The next council might address this issue with recommendations.

#### **Action:**

A new ACBSCT workgroup will be formed to develop recommendations regarding the effects of the costs of cord blood banking on the availability of this resource.

### *Cord Blood Distribution from Licensed and Unlicensed Banks*

Dr. Schriber asked about the number of cord blood centers that are licensed, are not licensed and plan to submit a BLA, or are unlicensed and do not plan to submit a BLA. Dr. Kurtzberg replied that five banks are licensed and two or three are preparing a BLA.

In response to a question from Dr. Schriber about the proportion of cord blood units distributed from licensed and unlicensed cord blood banks, Dr. Confer replied that about 97% of units distributed since 2011 have been under an investigational new drug (IND) application.

Dr. Milford asked about the number of high-quality units distributed that do not come from licensed banks and therefore are not eligible for reimbursement. Mr. Boo said that almost all units in the U.S. Registry meet the standards of the AABB (formerly the American Association of Blood Banks) and Foundation for the Accreditation of Cellular Therapy. Of the 20,000 cord blood units added to the U.S. inventory each year, about half are funded by NCBI. The NCBI units are used more frequently than the non-NCBI units, perhaps because many non-NCBI units have lower TNC counts.

Dr. Kurtzberg said that licensed banks and those preparing a BLA have banked fewer units in the last 2 or 3 years than in the previous 2 or 3 years with no difference in quality. However, because of the high cost of obtaining and maintaining licensure, licensed banks have less funding available to collect new units. Newer units seem to be used more often than older units. If units are added more slowly, this could affect usage.

Dr. Champlin pointed out that if cord blood banks now have 180,000 units and 97 percent would no longer be available once IND units can no longer be used, 175,000 units will no longer be available. Dr. Schriber said that the council can suggest that until the percentage of units from licensed banks reaches a certain level, the option of distributing IND units should remain available. Dr. Milford said that it will take a long time for a majority of units in the inventory to come from licensed banks.

### **Quality Issues with Umbilical Cord Blood for Transplant**

*Amanda Murphy, Department of Laboratory Medicine and Pathology, University of Minnesota*

Ms. Murphy summarized the results of a recent analysis of the quality of cord blood units that was a follow-up to a similar analysis conducted 10 years earlier. In the past 30 years, umbilical cord blood shifted from being regarded as biologic waste to a standardized product that can be licensed by the FDA. As in all blood banking, cord blood products distributed to patients must be of high quality. An analysis of units received at the University of Minnesota in 2001–2003 for transplantation found that about half had quality issues. The current study was designed to determine whether progress has been made in the units received for transplant between 2011 and 2013.

All cell products shipped to the university undergo a standardized review of quality. Concerns identified are categorized as related to medical history, quality control (QC)/quality assurance (QA), and labeling and documentation.

During the latest study period, the university received 249 cord blood units from 16 banks, primarily in the United States. Of these units, 159 (64%) had quality issues. The investigators identified 245 issues altogether, so the average number of issues per unit was 1.5. The 2001–2003 analysis included 246 cord blood units.

The proportions of units with quality issues in each of the three major categories were similar in both studies. In 2001–2003, rates were 40% for medical history, 54% for QC/QA, and 6% for labeling and documentation. In 2011–2013, rates were 48% for medical history, 49% for QC/QA, and 3% for labeling and documentation.

Many of the quality issues related to maternal medical or social history were unlikely to have an impact on unit quality or engraftment. Seven units had a quality issue related to QC/QA that was likely to have a clinical impact in the recent study, compared to 26 in the previous study. Very few paternal social history issues were identified, and most were unlikely to affect quality. The number of units with a labeling or documentation issue that could impair quality dropped from 15 in the previous study to 8 in the current study.

The proportions of quality issues in patients with an engraftment problem were similar in the two studies (28 percent in 2001–2003 and 25 percent in 2011–2013). Engraftment results were similar with units that did and did not have quality issues.

In conclusion, the recent study showed that the number of quality issues did not decrease between 2003–2003 and 2011–2013. However, the proportion of issues per unit and of units

with quality problems that were likely to have a clinical impact dropped significantly between the two study periods. Finally, the quality issues identified were not associated with engraftment problems.

### Discussion

Dr. Hartzman asked whether some hospitals refuse to pay for cord blood units with certain quality issues and therefore do not receive such units. Dr. McCullough replied that transplant coordinators might inform a cord blood bank of a quality issue with a unit and ask for a different unit, but this probably happens rarely. Most of the units received by the University of Minnesota come from licensed cord blood banks.

### **Trends in the Use of Haploidentical Transplantation**

*Mary Horowitz, M.D., Chief Scientific Director, CIBMTR*

Dr. Horowitz provided data on rates of haploidentical transplantation between 2010 and 2013 and discussed some recent and ongoing studies of this procedure.

#### *Recent Trends in Haploidentical Transplantation in the United States*

The number of first allogeneic HSCTs in United States increased steadily between 2010 and 2013. However, in 2013, more people had a transplant from an unrelated, matched donor than an HLA-matched sibling.

A sizable proportion of allogeneic HSCTs involve another type of transplant, such as double or single-cord blood, haploidentical, or HLA-unmatched. Virtually all haploidentical transplants involve 7 matched antigens. The distribution of graft sources has not changed much since 2010. Even in 2010, most transplants involved HLA-identical siblings or matched unrelated donors. However, slightly larger proportions of patients had haploidentical or single-cord transplants in 2013 than in 2010.

In Caucasians, the number of allogeneic HSCTs from matched, unrelated donors has increased slightly and from HLA-identical siblings has declined slightly. The total number of haploidentical cord blood transfusions also dropped, primarily because of a decline in single-cord transplants.

The number of allogeneic HSCTs in African Americans rose from 550 in 2010 to 600 in 2013. Transplants from HLA-matched siblings are much more common in this population than matched unrelated or haploidentical transplants, but the numbers of both types of transplants have increased. The rates of cord blood transplants (and of single- and double-cord transplants) in African Americans have been flat.

The distribution of graft sources is quite different in Caucasians and African Americans. Approximately 75 percent of Caucasians have an HLA-identical or matched unrelated donor. But fewer than half of African Americans undergo HSCT from an HLA-identical or matched unrelated donor.

The vast majority of patients who undergo HSCT in the United States are adults. The numbers of allogeneic HSCTs in children younger than 16 have remained flat, probably because of changes in the indications for transplantation. However, the number of cord blood transplants in children has dropped and of mismatched unrelated and matched unrelated transplants has risen. Trends in adults are similar.

### *Studies of Haploidentical Transplantation*

In 1990, haploidentical HSCT often resulted in graft-versus-host disease (GVHD) or graft rejection. A team of researchers at Johns Hopkins University pioneered an approach using cyclophosphamide to reverse graft rejection. This approach resulted in hematopoietic recovery and low rates of severe and acute GVHD. Although the results of the small studies conducted to date are encouraging, use of this approach is still in its infancy.

The Blood and Marrow Transplant Clinical Trials Network is conducting a multi-center, phase III, randomized trial (BMT CTN 1101) comparing reduced-intensity conditioning and transplantation of double unrelated umbilical cord blood to HLA-haploidentical related bone marrow transplantation for patients with hematologic malignancies. The study's primary endpoint is progression-free survival for 2 years. To date, the study has accrued 114 patients; the target is 410. Ancillary and co-occurring studies are a cost-effectiveness analysis (supported by an NHLBI R01 grant), an evaluation of an easy-to-read informed consent form, and the collection and storage of peripheral blood mononuclear cells for analysis of immune reconstitution.

A retrospective study (GS14-01) is comparing haploidentical and HLA-unmatched unrelated-donor transplants followed by cyclophosphamide for GVHD prevention in adults with AML who undergo standard myeloablative versus reduced-intensity conditioning regimens. The primary outcome is 2-year survival.

Haploidentical HSCT can be performed with lower GVHD and transplant-related mortality rates and acceptable 2-3-year overall mortality. The use of haploidentical HSCT is increasing, primarily in patients who lack an HLA-matched donor. But many issues still need to be studied, including the long-term outcomes of haploidentical HSCT, differences in efficacy by blood cancer, outcomes in children and in patients with nonmalignant disease, optimal graft type (bone marrow or peripheral blood) and preparative regimen, and relative efficacy compared to other donor sources. Although haploidentical HSCT is a valid option in patients without an HLA-identical donor, the data are insufficient to support recommending this approach over cord blood or HLA-mismatched unrelated-donor HSCT.

### Discussion

Dr. Campbell asked about the impact of the increased use of haploidentical transplants in African Americans on survival. Dr. Horowitz said that this impact is not known. Many changes have taken place in the past couple of years, and CIBMTR is collecting data on these changes.

Dr. Kamani commented that any transplant center can easily conduct haploidentical transplantation now that peripheral blood stem cells (PBSCs) are available. He was concerned that if the data ultimately do not support this approach, transplant centers will be unwilling to return to previously used approaches. Dr. Horowitz said that after a PBSC transplant, patients often achieve engraftment immediately and leave the hospital. They might return later with chronic GVHD, but they might also go elsewhere for GVHD treatment. As a result, transplant centers do not know the outcomes of this procedure.

Dr. Horowitz is concerned that the expense and difficulty of banking cord blood units will eliminate the opportunity to find out whether these transplants have better outcomes than haploidentical transplants. With more data on the use of high-risk matching to select the optimal unit, matched cord blood might have better results than HLA-matched transplants. But centers might start using haploidentical transplants before evidence is available to show that this is the best approach.

Dr. Rubinstein asked whether administering cyclophosphamide on the third day helps reduce GVHD risk. Dr. Horowitz said that this option is being explored in some settings. Dr. Laughlin urged transplant centers to be cautious about using such a strategy because of the lack of data.

## **New Business**

There was no new business.

## **Public Comment Period**

Shana Melius, M.B.A., M.A., of Preserve our Legacy administers a cord blood program at Harlem Hospital in New York City. The program has access to 30,000 women from ethnic minority groups throughout New York City. Ms. Melius asked how to help these women learn about cord blood banking options. Ms. Grant replied that HRSA informs expectant mothers of their options to privately or publicly bank cord blood, make units available for research, or treat these units as medical waste. Reaching out to individuals who can increase the diversity of the national registry is important. Ms. Grant suggested that Ms. Melius talk to the leaders of other cord blood banks in New York City.

Ms. Melius commented that African Americans have lower TNC counts than Caucasians. Raising the TNC threshold for cord blood would eliminate many potential African American donors. Finding a match is already difficult in this population, and a higher TNC threshold would make it even harder. Ms. Grant agreed that discard rates for African Americans and Asians would be higher if the TNC threshold rises. ACBSCT has considered how to inform expectant mothers about the likelihood that their units will be publicly banked.

## **Adjournment**

Ms. Grant thanked Dr. Milford for serving as ACBSCT chair for two terms.

Dr. Milford suggested that the council have a follow-up conference call to discuss the messages that the current council members will transmit to the new members.

**Action Item**

ACBSCT will hold a conference call to discuss the messages to transmit to the new council members.

Dr. Milford adjourned the meeting at 4:03 p.m.