ADVISORY COUNCIL ON
BLOOD STEM CELL TRANSPLANTATION (ACBSCT)
U.S. Department of Health and Human Services
NIH Fishers Lane Conference Center
Rockville, MD 20852

Friday, September 11, 2015

Welcome and Opening Remarks

Jeffrey McCullough, M.D., Chair, ACBSCT

Dr. McCullough called the meeting to order at 8:33 a.m. and welcomed all council members and other participants to the meeting.

Introduction of New Members

Patricia Stroup, M.B.A., M.P.A., Senior Advisor, Healthcare Systems Bureau, Health Resources and Services Administration (HRSA)

Patricia Stroup, M.B.A., M.P.A., introduced the new ACBSCT members: Helen Crawley-Austin, Beyond Consulting Solutions; Colleen Delaney, M.D., M.Sc., University of Washington; Marcelo Fernandez-Vina, Ph.D., Stanford University; Manish Gandhi, M.D., Mayo Clinic; Sergio Giralt, M.D., Weill Cornell Medical College; Mary Laughlin, M.D., Cleveland Cord Blood Center; and Elizabeth Shpall, M.D., The University of Texas MD Anderson Cancer Center.

Program Report

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

The Stem Cell Therapeutic and Research Act of 2005 authorized the C.W. Bill Young Cell Transplantation Program. The program was reauthorized in 2010, and its current authorization expires on September 30, 2015. The program's goals are to increase:

- The number of unrelated-donor transplants
- The recruitment of potential marrow donors
- Patient and donor advocacy services
- Public and professional education about transplantation
- Analysis and reporting of transplantation outcomes data

The C.W. Bill Young Cell Transplantation Program serves a growing number of patients needing unrelated donor transplantation. As of September 30, 2014, the program's registry included approximately 12.4 million adult donors, including more than 3.25 million racial/ethnic minority donors. The program is on target to meet its 2015 goal, which is to increase the number of racial/ethnic minority donors to 3.5 million.

The total number of cord blood units (CBUs) available through the program in FY 2014 exceeded 200,000. The program facilitated 960 cord blood transplants in FY 2014 (a 13%

decrease from FY 2013) and shipped 1,359 CBUs (a 13.7% decrease from FY 2013). The program's appropriations since FY 2013 have been steady at a time when many other federal program budgets have declined.

Balancing the use of program and National Cord Blood Inventory (NCBI) funds is important because Congress expects all authorized functions of the program and NCBI to be successful. Program staff therefore do the following:

- Conduct cord blood bank site visits to better understand the banks' needs
- Conduct site visits to transplant centers, donor centers, apheresis centers, and recruitment organizations to observe and better understand the roles and needs of the organizations that facilitate unrelated blood stem cell transplants
- Provide financial support for FY 2016 (through the Cord Blood Coordinating Center) to select NCBI banks that will make cord blood units more rapidly available through the program
- Identify special projects to increase the number of CBUs collected annually and the number of umbilical cord blood transplants
- Balance the use of NCBI funds across the 13 cord blood banks with NCBI contracts
- Give priority funding to:
    - Cord blood banks that collect a higher percentage of minority units, have obtained a Food and Drug Administration (FDA) biologics license, offer the government significant discounts, or expand cord blood collections
    - Maintenance of the financial stability of cord blood banks

Current priorities for public cord blood banking are as follows:

- Continue building the public inventory and meeting the needs of diverse patient populations and the statutory goal for inventory size
- Ensure continued access to cord blood as a source of blood stem cells
- Understand the reasons for the decrease in cord blood use
- Assess current initiatives established to help increase CBU collection and transplantation
- Establish a remote collections pilot project
- Expand cord blood collections at new or existing hospitals
- Form a task force to assist with difficult or stalled patient searches
- Establish new initiatives in consultation with the ACBSCT and other Department of Health and Human Services (HHS) agencies

Discussion

Thomas H. Price, M.D., asked whether HRSA collects details on the numbers of NCBI-funded cord blood banks that are collecting more or fewer CBUs than in the past. Ms. Grant said that HRSA does not collect these data. She added that at times, cord blood banks intentionally collect fewer CBUs for a given period so that they can focus on another goal, such as obtaining FDA licensure. Decreases in CBU collection are permitted under these circumstances.

Overview of Past Recommendations

Patricia Stroup, M.B.A., M.P.A., Senior Advisor, Healthcare Systems Bureau, HRSA
Shelley Grant, M.H.S.A., Chief, Blood Stem Cell Transplantation Branch, Division of Transplantation, HRSA

Ms. Stroup explained that the ACBSCT, a federally chartered advisory council, is charged with reporting to the Secretary of HHS on a variety of scientific issues related to hematopoietic stem cell transplantation (HSCT). The council had its first meeting in 2008, and the current meeting was its 15th.

Ms. Grant explained that when the ACBSCT last met in September 2014, Sylvia Mathews Burwell had just become Secretary of HHS. The ACBSCT decided to send Secretary Burwell a list of the council's 26 recommendations to date and the status of each. Because the ACBSCT has many new members this year, Ms. Grant summarized each recommendation and the actions taken to implement it (see the appendix).

Discussion

In response to a question from Ms. Crawley-Austin about Recommendation 3 (Centers for Medicare & Medicaid Services [CMS] national coverage determination on allogeneic stem cell transplantation for myelodysplastic syndromes [MDS]), Ms. Grant explained that HRSA had shared data with CMS on transplantations for MDS not covered by CMS. The number of transplantations would grow if CMS provided coverage. Jeffrey R. Schriber, M.D., commented that the change in CMS policy regarding coverage of HSCT for MDS has been a huge success.

Ms. Grant answered a question about the federal programs referred to in Recommendation 10 (recognition of HSCT as a covered benefit) by explaining that the most relevant programs are Medicare and Medicaid. Another opportunity is to engage the Office of Personnel Management, which oversees benefits for all federal employees because many other insurance plans emulate the federal plans. Dr. Schriber pointed out that private insurance plans also follow the lead of Medicare and Medicaid.

Commenting on Recommendation 11 (Medicare reimbursement for the acquisition of blood, bone marrow, and cord blood products for HSCT on a cost basis), Dr. Schriber stated that the current system provides a major disincentive for the many small centers that are not Medicare exempt. This issue should be a priority for the ACBSCT.

Andrew D. Campbell, M.D., asked whether HRSA would review gene therapy for sickle cell disease (SCD) and thalassemia. Ms. Grant replied that HRSA focuses on transplantations involving a donor.

Dr. Laughlin remarked that a recommendation on gene editing from the ACBSCT would be very timely. Another recommendation on myeloablative autologous transplantation (known as gene therapy) would also be very timely.

Stem Cell Sources for Unrelated HSCT

Umbilical Cord Blood

John Wagner, M.D., University of Minnesota

The collective goals of HSCT, regardless of stem cell source, are prompt hematopoietic recovery, minimal transplantation-related mortality with retention of a graft-versus-leukemia (GVL) effect, high cure rates without late effects independent of human leukocyte antigen (HLA) match, and worldwide transportability.

An advantage of peripheral blood and bone marrow stem cells is the extensive experience using these sources. However, they have some challenges, including the lack of donors with 8/8 matched HLA markers for all patients and the risk of graft-versus-host disease (GVHD). These challenges are being addressed through the use of alternative stem cell sources.

In the early 2000s, the use of cord blood for HSCT took off. One reason was animal studies showing that HSCT with cord blood resulted in similar leukemia-free survival to HSCT with matched bone marrow stem cells and that cord blood transplant had a low risk of GVHD and relapse. Patients who undergo cord blood transplantations with mismatched markers can have very good outcomes.

An initial study of double cord blood transplantation had very good results, including a low relapse rate. However, a more recent study of double cord blood transplantation found that double cord blood transplantation did not improve survival compared to single cord blood transplantation. More research (including economic analyses and quality-of-life studies) is needed on the risk of GVHD and relapse-free survival by stem cell source.

Advantages of cord blood include high donor safety, rapid availability, extensive experience (40,000 transplants to date), and comparable outcomes to 8/8 matched HLA transplantation with peripheral blood or bone marrow. However, cord blood transplantation is more expensive than transplantation with other sources. Graft costs for cord blood transplantation are as much as $40,000 higher than for peripheral blood/bone marrow transplantation (BMT) and up to $50,000 more than haploidentical HSCT. Cost drivers include inefficiencies in collection and payment for unused units, delayed hematopoietic recovery, graft failure, regulatory burden, and licensure requirements.

Disadvantages of haploidentical HSCT include its status as a “boutique strategy” requiring intensive chemotherapy and radiation, high stem cell doses, and graft manipulation. This procedure is associated with high rates of transplant-related mortality and infections. Although some centers have had excellent outcomes from haploidentical HSCT, other centers have not. Johns Hopkins University developed a haploidentical HSCT approach that can be used by other centers, can be rapidly implemented, has no regulatory burden, is relatively cheap, and has very low rates of transplant-related mortality. Dr. Wagner questioned whether licensure has enhanced safety.

The jury is still out on whether haploidentical HSCT is preferable to HSCT using cord blood. If disease-free survival and late effects are equivalent, the cheapest option is best. Questions that need to be answered include:

- Is it possible to identify the best HSC source or to eliminate an HSC source?
- What are the most cost-effective investments for making transplantation more effective and accessible?
- What can be eliminated to reduce costs without compromising safety?

Graft failure is the most costly HSCT complication. Patients who have a relapse die more quickly. Retrospective comparative trials are needed, and a trial is needed to compare cord blood, haploidentical, and peripheral blood HSCT. In the meantime, research needs to address the limitations of each HSC source.

Tough questions to answer are:

- Is cord blood needed?
    - If the answer is not known, how could the question be answered?
    - If cord blood is needed, is the current banking model the right one? What is the target number of units? Why is use dropping?
- Are licensure and investigational new drug applications (INDs) necessary to improve quality and safety?
    - If the answer is unknown, the added costs need to be justified.
    - If licensure and INDs are necessary, is it possible to minimize the impact on costs?

Discussion

Dr. Laughlin explained that Medicare, Medicaid, and private insurance plans pay to treat patients for blood-related cancers. However, transplant physician focus on 100-day bundled costs. Clinicians can make decisions about renal transplants without considering the cost of the graft, which is not part of the bundle. The GVL effect of cord blood transplantation is impressive, especially in lymphoid malignancies. Dr. Wagner agreed that cord blood, especially double cord blood transplantation, has a risk of GVL effect. In adults undergoing double cord blood transplantation, the graft accounts for 30% of the transplantation cost, which is disproportionate. Separating the graft cost from the other costs would change the dynamic. Many transplant centers are under pressure to reduce cord blood transplantation because of its expense.

Dr. Giralt wondered what would happen if all of the current cord blood inventory could be used as a result of new technologies. Dr. Wagner said that if cell dose decreases, it is possible to find a better matched donor for every patient. Dr. Giralt stated that in most large transplant centers, donor availability is no longer a barrier to access, but only 30% of those who would benefit from HSCT are undergoing this procedure for financial and other reasons. These other factors need to be identified and targeted.

Mismatched Unrelated Donors
Dennis L. Confer, M.D., Chief Medical Officer, National Marrow Donor Program (NMDP); Associate Scientific Director, Center for International Blood and Marrow Transplant Research (CIBMTR)

There are no head-to-head comparison data on different sources of mismatched unrelated donor HSCs. The existing data come from single centers or a few centers and are subject to selection bias. No randomized studies have been completed, and such studies would be logistically challenging. The optimal practices for each graft source are continuing to evolve.

Dr. Confer focused his remarks on HLA matching, including for high-expression loci (A, B, C, and DRB1) and low-expression loci (DRB3, DRB4, DRB5, DQ, and DP). He did not plan to address other important considerations, such as donor age or ABO status.

Studies have shown that 9/10 matched transplantations have poorer survival than transplantations with 10/10 matched grafts. A single mismatch or a second mismatch at HLA-DQ, however, does not increase risk compared to 10/10 matching loci, and matching for HLA-DQ does not have a significant effect on survival after unrelated donor HSCT.

Mismatches in C*03:03/C*03:04 alleles (the predominant allele-level mismatch in patients and donors of European ancestry) are most common among transplants with a single allele-level mismatch in HLA-C. Outcomes in patients receiving 7/8 C*03:03/C*03:04 mismatch transplants are not significantly different from those with 8/8 HLA matched transplants. Therefore, if a mismatched HSC source must be considered, a C*03:03/C*03:04 mismatch is more acceptable than other alternatives.

The low-expression HLA class II loci encode for products that are expressed at low levels. A study showed that three or more mismatches at HLA class II low-expression loci are associated with poor clinical outcomes after 7/8 matched transplantation. However, no single low-expression locus seemed to have a greater effect on clinical outcomes when mismatched than other low-expression loci.

Unidirectional graft-versus-host vector 7/8 HLA mismatches have the same risk as bidirectional 7/8 mismatches. For HLA homozygous recipients, a mismatch at the homozygous locus is preferable to a mismatch at the heterozygous locus because it is associated with a lower risk of acute GVHD than other 7/8 mismatches and does not increase graft failure risk.

Most transplant candidates have a 7/8-matched unrelated donor. These transplants have a higher risk of GVHD and transplant-related mortality, leading to lower overall survival. These impacts are most evident in early-stage disease. However, some patients who undergo 7/8 mismatched transplantation have long-term, disease-free survival. Strategies focused on low-expression loci (DQ, DP, DRB3, DRB4, and DRB5) may improve outcomes.

Discussion

Dr. Giralt asked whether centers use this information in their donor-selection algorithm. Dr. Confer said that many centers are not aware of these data. Other centers are aware of these data, but Dr. Confer did not know how many centers have incorporated this information into their algorithms. Dr. Giralt emphasized the need to find out how many centers have adjusted their algorithms based on this information, and Dr. Confer suggested that this information might be available from CIBMTR.

Dr. Schriber commented that considerations of costs must include long-term issues, such as chronic GVHD, lost days of work, relapse, and mortality. These costs might be different in patients with low-risk versus high-risk disease.

Related Haploidentical BMT
Richard Jones, M.D., Director, Bone Marrow Transplantation Program and Professor of Oncology, Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins

Most people needing a transplant do not have an HLA-matched sibling. Initially, mortality rates for mismatched transplants exceeded 50%, mostly due to GVHD. G.W. Santos and A.H. Owens explored the use of high-dose cyclophosphamide as an alternative conditioning regimen to total body irradiation for haploidentical transplantation based on this regimen's immunosuppressive properties. Relapse rates with this approach in patients with leukemia were high, so they added busulfan.

A clinical trial showed that high-dose cyclophosphamide is immunoablative but allows rapid hematopoietic and immunologic recovery in autoimmunity. The 5-year actuarial survival rate was 91%, the event-free survival rate was 21%, and patients had no opportunistic infections. Other trials showed that in patients with leukemia or lymphoma and no suitable related donor, HLA-haploidentical related-donor BMT with high-dose cyclophosphamide prevented acute GVHD and reduced the incidence of chronic GVHD. The non-relapse mortality rate was low, and the overall survival rate was good. Furthermore, this approach does not require consideration of degree of HLA matching when choosing a donor, transplants from second-degree relatives work as well as those from first-degree relatives, and immune recovery rates are excellent. Several international groups have confirmed these results.

Dr. Shpall and her colleagues showed that both T-cell depletion and post-transplantation cyclophosphamide prevent GVHD. However, T-cell depletion could impair immune cell recovery. T-cell depletion might be most effective for children and young adults whose thymus can reconstitute T cells from stem cells, but it might not work well in adults whose thymus is no longer functional.

The use of high-dose cyclophosphamide results in few opportunistic infections, and outcomes of haploidentical transplantation using high-dose cyclophosphamide do not differ by age. The only factor that predicts how well a patient does is disease risk index. Haploidentical and matched transplantations with high-dose cyclophosphamide have similar outcomes in patients with lymphoma or leukemia.

Today, an 8/8 match should no longer be the gold standard, and no patient needing a transplant should be denied one. Results with alternative donors might be similar to or even better than those for matched siblings in some cases (e.g., when the sibling is unhealthy or is older). If Dr. Jones must choose between an unhealthy matched sibling and a healthy haploidentical donor, he chooses the healthy haploidentical donor. Finally, the use of alternative donors gives minorities equal access to a transplant.

Dr. Jones believes that it is time to stop the GVHD/GVT vicious cycle, in which approaches that lower rates of GVHD increase relapse rates and vice versa. No "rheostat" exists for reducing rates of both GVHD and GVT effect. However, combining a nontolerant alloimmune system with novel anticancer agents might promote GVT without the toxicity of GVHD.

Discussion

Mark Walters, M.D., said that in nonmalignant conditions, GVHD is a leading cause of transplant-related mortality. He suggested using the GVHD prophylaxis approach that Dr. Jones had described for nonmalignant conditions. Dr. Jones agreed. Naynesh R. Kamani, M.D., thought that Dr. Jones's approach might not be appropriate for nonmalignant conditions, especially hemoglobinopathies. Graft rejection is a major problem in SCD and, probably, in thalassemia.

Claudio G. Brunstein, M.D., Ph.D., reported that a national randomized study will collect data on the costs for payers and patients of cord blood and haploidentical transplantation over 2 years. These data will provide a picture of costs immediately after the transplantation and the longer-term complications.

Dr. Laughlin said that HSCT is very expensive, but this cost is justified by the fact that it is a one-time, curative therapy. Dr. Jones's proposal to use HSCT as a platform for other therapies would increase the cost. Dr. Jones reported that the cost of transplantation varies by center. Most transplantations at Hopkins are conducted on an outpatient basis and are cheaper than many novel therapies. The most important economic factor when determining whether to add therapies to transplantation is whether doing so will cure the patient.

Economics of Cord Blood

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

Mr. Boo highlighted the following trends in the use of various transplant sources:

- The use of cord blood increased substantially starting the early 2000s before dropping off in the last 2 years. However, cord blood use increased in 2015, perhaps because of research data published in 2014 showing that single cord blood transplants have equivalent results to double cord blood transplants.
- Peripheral blood stem cells have become the primary source of related HSCT.
- Cord blood is used more frequently in pediatric patients and those from minority groups.

- The number of transplants for adult patients has been stable in the last 5 years but declined in pediatric patients. However, pediatric use of cord blood increased 19% in 2015.
- The number of mismatched unrelated and haploidentical transplants rose between 2010 and 2013.

Inventory analysis has shown the following:

- The NMDP domestic cord blood inventory has grown steadily since 2005, with about 15,000 new units added each year.
- During this period, the inventory of CBUs with less than 90 x 10^7 total nucleated cell (TNC) count has dropped slightly, whereas the inventory of all other segments, especially the 90 x 10^7 to 124 x 10^7 segment, is growing with the assistance of NCBI.
- The largest CBUs are shipped most frequently, partly because most patients undergoing transplantation are adults, who typically need larger units. For example, for a single cord blood transplant, most Caucasian adults require a unit with at least 150 x 10^7 TNC count.
- African American patients are mostly likely to find a match for a 90 x 10^7 to 124 x 10^7 unit within their own race. However, fewer African American units are available for patients needing larger units. Caucasians can find larger units from Caucasian donors more easily.

Financial modeling findings based on data from four banks include the following:

- In 2015, CBUs yielded approximately $44.5 million in revenue and their total costs were about $62 million, resulting in a net loss to the cord blood banking industry even with the HRSA subsidy of approximately $10 million.
- Based on current cord blood use, losses are likely to grow over time.

One way to help cord blood banks to break even is to raise the TNC count threshold for banked units. The collection and storage of unused CBUs is costly, and reducing the number of CBUs collected by raising the TNC threshold would increase efficiency and make the industry sustainable. Furthermore, sufficient inventories of smaller units are available to sustain choice for several years. If the threshold rose, banks would be able to collect more large units, which are the most likely units to be selected, because they would no longer spend money building inventories of small units.

Discussion

Dr. Laughlin commented that TNC counts are lower in CBUs from African Americans, and banks collect fewer units from African American donors. She asked about the effect on units from African Americans if the TNC threshold were raised. Mr. Boo said that if the threshold were raised, banks would need to use strategies that ensure the availability of enough units for African Americans.

Cord Blood Workgroup Update

Thomas H. Price, M.D., Professor of Medicine, Division of Hematology, University of Washington School of Medicine

The Cord Blood Workgroup has a narrow charge, to revisit the issue of the HRSA TNC threshold for reimbursement. Currently, HRSA only subsidizes the banking of NCBI CBUs if the TNC count meets or exceeds the minimum threshold of 90×10^7. Banking such small units that are rarely used is financially unsustainable and therefore threatens the continued existence of cord banks. Only about 2% of a bank's inventory of units with a 90×10^7 to 124×10^7 TNC counts are ever used. Use increases as TNC counts rise.

Reasons to raise the threshold include the unintended consequences of the current threshold, which encourages banking of smaller units. Some banks are reluctant to forgo HRSA funding and continue to bank smaller units. Furthermore, banks must sometimes collect smaller units to meet mutually agreed-on HRSA quotas. However, 8–15% of patients do use UBC units with a TNC count lower than 125×10^7, and use is highest among minority patients. Failure to continue to bank small units might adversely affect the ability of minority patients to find a suitable cord blood source. But the inventory of small units is huge and will continue to be available if the HRSA threshold rises. Furthermore, minority patients do not need more small units; they need more large, diverse units. Raising the threshold and the per-unit subsidy would probably accomplish this goal.

The workgroup supported the shift to larger units, especially from minority donors, and the preservation of access to suitable CBUs for minority patients. The shift to a higher TNC threshold should be gradual and part of a comprehensive strategy for recruiting, collecting, and banking CBUs that could vary from bank to bank. A new ACBSCT workgroup could be established to determine how to substantially increase the recruitment of donors, especially those from minority groups, to ensure that banks collect enough diverse units with high TNC counts. The group would also explore ways to fund these strategies.

Discussion

Dr. McCullough thanked Dr. Price and the workgroup for their recommendations. He asked council members whether they agreed with the workgroup's proposal. If so, the council would form a new workgroup to identify strategies for increasing the number of large units that cord banks collect. HRSA has indicated that it is open to working with this new group and finding ways to provide financial support for new strategies to collect more large units.

Dr. Price said that when cell expansion is available, large units will be less important. However, it is unclear when cell expansion will be widely available, and this is not likely to occur for several years.

Dr. Kamani said that the data clearly show that the current threshold is not financially sustainable in the long run and needs to be changed. However, any strategies to change the threshold must ensure that units are sufficiently diverse to preserve access for minority patients.

Robert Hartzmann, M.D., commented that the fact that cord banks are not currently collecting more large units is a sign that doing so is not important. Joanne Kurtzberg, M.D., pointed out that cord blood banks are strapped for money and have spent a great deal of money to obtain licensure. Banks need HRSA reimbursement on a per-unit basis to subsidize larger units with equivalent diversity that require many more collections. The proposal will result in the addition of fewer units to the inventory, but those units are more likely to be used. Under the current system, banks would need to give up HRSA subsidies to raise the threshold, which would compromise their financial health. One suggestion is to view every patient as a donor and ask all mothers to sign a simple consent form. This approach reduces collection costs.

Dr. Price noted that some banks have raised their thresholds and are continuing to lose money. Several banks have cut back their collections to save money, and some do not collect new units at all. This is not a desirable situation.

Dr. Laughlin commented that in addition to having lower TNC counts, minority units have other issues, such as higher infectious disease rates. This raises the costs of collecting units from minority donors.

Innovative Uses of Cord Blood

Ex-Vivo Expansion of Cord Blood Stem/Progenitor Cells for Clinical Application

Colleen Delaney, M.D., M.Sc., Associate Professor, Department of Pediatrics, Division of Pediatric Hematology/Oncology, University of Washington

Clinical outcomes for alternative donor transplants have improved significantly. However, the choice of the right stem cell source still depends on many factors. For cord blood transplantation, in particular, many barriers still need to be overcome in spite of data showing that their outcomes are equivalent to those of matched unrelated donor transplants. Current hurdles to cord blood transplantation include the costs associated with donor cell grafts and with cord blood transplantation because of delayed engraftment and immune reconstitution as well as the need for more intensive supportive care.

The increasing use of haploidentical HSCT is probably due to the fact that the first 100 days after this type of transplantation are easier, whereas the first 100 days after cord blood transplantation are difficult and patients need more intensive supportive care during this period. Patients with delayed engraftment have a higher risk of mortality than those with earlier engraftment. However, the risk of relapse is much lower after cord blood transplantation than after transplantation with units from matched or mismatched unrelated donors. Disease-free survival rates are similar for cord blood and for matched or mismatched unrelated donor transplantation.

Dr. Delaney and others have shown that ex vivo cell expansion can dramatically decrease the time needed for engraftment. Dr. Shpall has pioneered a mesenchymal stem cell expansion system for real-time expansion while the patient is undergoing conditioning. Now that its effectiveness has been demonstrated, the researchers need to make the approach easier. The goal is to provide rapidly engrafting cells that produce rapid neutrophil recovery, which should improve overall survival while reducing costs.

In a pilot study in 15 patients, Dr. Delaney's cell-expansion protocol resulted in engraftment at 19 days compared to 25 days from conventional CBUs, and platelet engraftment was superb. Only two patients died due to relapse, and there were no transplant-related deaths or grade 3–4 GVHD. Additional benefits beyond engraftment included fewer days in the hospital and fewer infections.

An ongoing multicenter, open-label, randomized study is comparing single or double myeloablative cord blood transplantation with or without infusion of off-the-shelf ex vivo expanded cryopreserved cord blood progenitor cells in patients with hematologic malignancies. This study will assess whether the ex-vivo expansion techniques allows the use of smaller units for transplantation and avoids the need for double-cord blood transplantations. This approach would reduce costs and might be able to move the rheostat by reducing the risk of GVHD without increasing relapse risk.

Discussion

Dr. Kamani asked whether the ex-vivo expansion approach would be less costly than a double-cord blood transplant. Dr. Delaney replied affirmatively. In response to a question from Dr. Schriber, she added that the next trial will compare single cord blood transplants using the ex-vivo expansion product to double cord blood transplantation.

Other Uses of Cord Blood
Claudio G. Brunstein, M.D., Ph.D., Associate Professor of Medicine, University of Minnesota Medical School

Umbilical cord blood is made up of progenitor and stem cells, immune regulatory and effector cells, and mesenchymal cells and progenitors. A large inventory is available of cord blood-derived products, and HLA typing is possible. Validated methodologies have been developed to separate cells into subpopulations and grow them. Cord blood donation does not require time off work, and more than 600,000 units are banked worldwide. It is possible to make patient-directed products from a second or third unit or use a portion of a unit. Another option is to use an off-the-shelf product. Expansion methodologies are improving, and it is now possible to expand cells more than 1,000 fold.

Barriers to successful allogeneic transplantation include graft rejection/aplasia, GVHD, immunological reconstitution, and relapse of malignancy. Cord blood-derived products can address some of these barriers. For example, myeloid progenitors are indicated for bone marrow aplasia and are used for transient or permanent repopulation. They are currently being investigated in phase 1 and 2 clinical trials.

Regulatory T (Treg) cells "calm down" the immune system instead of creatoxin alloreactivity, so that the patient's T cells are not deadly when they are activated. Treg cells can be used in people with immune dysregulation, they can suppress GVHD, and they have the potential to treat autoimmunity. Treg cells are easy to separate out from cord blood, and they are being expanded at the University of Minnesota. A phase 1 dose-escalation study that has now enrolled 12 patients

found that multivirus-specific T cells from cord blood reduced Epstein-Barr viral, cytomegaloviral, and adenoviral load. Treg cells are undergoing investigation in phase 1 clinical trials of GVHD.

Natural killer cells are used to treat malignancy and prevent relapse, and they are being investigated in a phase 1/2 clinical trial. Cord blood is the source of natural killer cells in some studies. Their activity depends on a balance between activating and inhibitory signals. Natural killer cells have shown activity in acute myeloid leukemia, MDS, non-Hodgkin's lymphoma, multiple myeloma, and ovarian carcinoma. The focus is on allogeneic natural killer cells because autologous natural killer cells have failed before and might not be healthy after chemotherapy. Cord blood-derived natural killer cells have shown activity against myeloma.

Discussion

Dr. Confer wondered whether the potential to use cord blood for other products could be the "savior" for cord blood banks. Dr. Brunstein explained that the approaches he discussed are not close to broad clinical use. Dr. Delaney added that if the technologies advance, small units could be used to develop the products that Dr. Brunstein had described.

Dr. Kurtzberg said that some of the technologies discussed and others in development will provide other uses for banked cord blood. Autologous cord blood is being used for brain injury in children, and allogeneic cord blood studies are ongoing in adults with stroke. If these techniques take off, the cord blood inventory will have much broader uses.

Dr. Giralt asked about the economics of expanding cord blood. Dr. Delaney said that the vision is for the expanded cells to be distributed like a drug to transfusion centers and hospitals and not through a banking system. The current formulation is a 20 cc aliquot that is infused intravenously. Ideally, the product will show effectiveness in chemotherapy-induced neutropenia. Dr. Delaney's product has not undergone economic analyses, but the 75% of CBUs that are not useful for banking could be useful for this technology.

New Business

American Society for Blood and Marrow Transplantation (ASBMT) Letter

Dr. Shpall read aloud a letter she and Juliet Barker, M.D., had written to Dr. McCullough on behalf of the ASBMT Cord Blood Special Interest Group and ASBMT Executive about the financial challenges in funding public cord blood banks in the United States. They note that cord blood transplantation can cure some otherwise lethal diseases of blood and bone marrow and is especially important for patients who lack other suitable stem cell donors. The availability of this life-saving source is compromised by the increasing costs of public cord blood banking. The letter notes that increased federal funding is needed to ensure ongoing and, ideally, improved access to adequately dosed, publicly donated cord blood units. Drs. Shpall and Barker urge the ACBSCT to address this issue and provide its strongest support for increased funding of public cord blood banks.

Dr. Kamani commented that several obstetric societies are recommending delayed clamping of the umbilical cord at delivery, which could reduce the TNC count of the resulting CBU. Dr. Hare said that this practice has only been shown to be beneficial in premature infants born earlier than 34 weeks of gestation. Dr. McCullough added that this practice should not prevent the ACBSCT from moving forward with plans to support the ASBMT request.

Recommendation to Raise the TNC Threshold

Dr. McCullough asked the council to consider the following potential recommendation:

> Recommend that HRSA work with the NCBI banks and the blood stem cell transplantation community to develop recruitment and collection strategies that will result in banking cord blood units (CBUs) with the highest possible total nucleated cell (TNC) count without impairing access for racial and ethnic minorities needing cord blood transplantation. If data support the shift to a higher TNC threshold for CBUs, the shift should be gradual and part of a comprehensive strategy for recruitment, collection, and banking that might vary from bank to bank.

Dr. McCullough said that if the council agrees that the TNC threshold for CBUs should be raised, it will form a workgroup to discuss the optimal strategies for accomplishing this goal and whether different populations require different thresholds or strategies. He agreed in principle with the need to raise the TNC threshold.

Joanie Y. Hare, M.D., asked what threshold should be used for African Americans, who tend to have lower TNC counts. Dr. Kurtzberg said that the criteria for transplant selection do not differ by race/ethnicity, and all patients regardless of race need a high cell dose with a close HLA match. This is more difficult to achieve for minority groups for many reasons, including HLA diversity and the difficulty of collecting high cell doses from minority donors. Increasing the number of collections is one way to obtain an equivalent inventory with racial diversity and high TNC counts. Dr. Kurtzberg argued strongly against using different criteria or definitions of quality by race.

Ms. Grant explained that physicians always try to collect as many stem cells as possible for each CBU. The rates of collection and discard would need to be much higher if the threshold were raised, and expectant parents would need to be properly informed about the likelihood that their units would be used.

Dr. Wagner stated that the reason for increasing collections of units with high TNC counts is to ensure that adequate grafts are available for large adults. Many patients are not large, however, and excluding the collection of small units would limit the HLA diversity that could benefit smaller people, including children.

Mr. Boo explained that capturing the greatest diversity for every potential patient can burden the industry with a task that decreases its opportunity to create a meaningful inventory for the greatest number of patients. Mr. Boo supported the recommendation to raise the TNC threshold, but he noted that efforts to increase TNC count should not harm those who benefit from the

broad inventory. If the industry is not sustainable, no one will have access to cord blood transplants.

Dr. McCullough asked if any ACBSCT members disagreed with the need to raise the TNC threshold, and no one expressed disagreement. The council therefore adopted the recommendation.

Dr. McCullough announced that Mary C. Hennessey, J.D., and Karen Ballen, M.D., have agreed to chair the new workgroup. Members will include Ms. Crawley-Austin and Drs. Hare, Shpall, Kurtzberg, and Price.

Recommendation for CMS Reimbursement on a Cost Basis

Dr. McCullough asked the ACBSCT to consider this potential recommendation:

> That the Secretary encourage the Centers for Medicare & Medicaid Services (CMS) to reimburse for the acquisition of blood stem cells, bone marrow, or umbilical cord blood products for hematopoietic stem cell transplant on a cost basis, consistent with CMS guidelines for solid organ transplants.

The ACBSCT agreed with this recommendation.

Susan Stayn, J.D., asked what the council can do to support efforts to obtain CMS reimbursement for myeloma and other important conditions that can benefit from HSCT. The lack of reimbursement is limiting access. Mr. Boo described the NMDP plan to discuss this issue with CMS again in the fall. If these discussions are not successful, the ACBSCT will assess potential next steps.

Human Subjects Research

Ms. Stayn reported that HHS had released a notice of proposed rulemaking that would change the federal rules for all human subjects research, including federally funded research. She wondered whether the council should consider how this new rule could affect research related to HSCT. Dr. Kamani said that this proposed rule is open for public comment, and the government will take these comments into consideration in drafting the final rule. He was not sure how the ACBSCT could influence the HHS decision.

Hemoglobinopathies

Stem Cell Therapies for SCD
Mark Walters, M.D., Benioff Children's Hospital

Some experts believe that more research is needed on the risks of HSCT for SCD. However, an international expert panel recently concluded that young patients with symptomatic SCD who have an HLA-matched sibling donor should undergo transplantation as early as possible,

preferably at preschool age. In addition, they recommended unmanipulated bone marrow or cord blood from matched sibling donors as the stem cell source.

In a study that enrolled 59 children with SCD, matched sibling allograft transplantations resulted in a 93% overall survival rate and an 83% event-free survival rate. The cumulative incidence of graft rejection was about 15%. Since this study was published more than a decade ago, HSCT has been used in patients up to age 20. In a study of 195 pediatric patients who underwent an HLA-matched sibling allograft transplantation, the overall survival rate was 95%, the SCD-free survival rate was 92%, and only 3 of 180 survivors were receiving immunosuppressive treatment for GVHD at last followup. Graft rejection and chronic GVHD are not major problems with matched sibling donor HSCT. However, a Belgian study in 469 patients found that mortality rates were significantly higher for HSCT with identical or cord blood grafts than hydroxyurea. For this reason, Dr. Walters takes issue with the recommendation of the SCD expert panel.

Dr. Walters listed several barriers to HSCT in SCD. Only 14% of families have an HLA-matched sibling donor, only 19% have a well-matched unrelated donor, and clinicians do not refer patients for HSCT because of the risk of GVHD and death. Dr. Walters addressed these barriers in a pilot trial of HLA-matched BMT for adults with SCD, in which 21 of 22 participants survived free of SCD. A followup study is comparing HLA-matched BMT and standard care in adults with SCD. He is also developing a study of haploidentical BMT in adults and children with SCD.

A new BMT study in the Bone and Marrow Transplant Clinical Trials Network (BMT CTN) will assess prevention of SCD-related complication in 200 patients. Patients who have an HLA-matched donor will be assigned to transplantation. Those lacking a donor will make up the comparison cohort. This will be the first trial to compare transplantation to no transplantation in equivalent groups of patients.

Another BMT CTN study will assess reduced-intensity conditioning before HLA-haploidentical BMT in patients with symptomatic SCD. The study will use the same regimen as that described by Dr. Jones earlier in this meeting.

In summary, HSCT for SCD in children is performed rarely and is generally used only in children with significant complications. The broader use of HSCT in children with a suitable sibling donor results in similar survival to supportive care. Studies that might expand HSCT to adults and the use of haploidentical donors are in development.

Discussion

Dr. Laughlin commented that a trend throughout pediatrics, especially in nonmalignant hematology, is to move away from myeloablative conditioning because of its toxicity and effects on fertility, but gene therapy uses this conditioning regimen. Dr. Walters explained that gene therapy trials are restricted to adults who undergo gamete cryopreservation, and the concerns that Dr. Laughlin mentioned must be addressed before this treatment is expanded to children. Perhaps myeloablation, which carries a risk of MDS and acute myeloid leukemia, will not be necessary in the future.

Dr. Campbell asked whether adults with SCD have a higher risk of chronic GVHD after HSCT than children. Dr. Walters replied that different regimens are used in adults and children, and outcomes are similar in young adults and children with a matched-sibling donor.

Dr. Kamani believes that gene therapy for SCD is exciting, but a therapy that is effective is available and underused. The focus should be on BMT, not gene therapy.

Workgroup Report: Advancing HSCT for Hemoglobinopathies
Naymesh Kamani, M.D., Division Director, Division of Cellular Therapies, AABB Center for Cellular Therapies

The ACBSCT created a workgroup to advance HSCT for hemoglobinopathies in 2012. The workgroup's charge remains to identify barriers to transplantation, identify opportunities to more fully realize its potential for individuals with SCD and thalassemia, and submit for consideration and adoption by the ACBSCT recommendations for high-priority actions.

The many reasons why transplantation is underused in SCD include the following:

- Disease related:
    - Heterogeneous nature of the disease and lack of clinical/laboratory/genomic predictors of poor prognosis
- Patient/family related:
    - Fear of transplant-related mortality and morbidity
    - Fear of risk of long-term complications (GVHD and infertility)
    - Comfort with transfusion programs for those with complications
    - Gaps in knowledge about natural history and progressive organ damage
    - Mistrust of medical professionals
- Health care provider related:
    - Provider reluctance to recommend HSCT
    - Gaps in knowledge about the role of HSCT
- Donor availability related:
    - Lack of matched sibling donors
    - Lack of well-matched unrelated donors for the majority of patients
- Insurance coverage related:
    - Gaps in coverage

The workgroup has focused on lack of insurance coverage and awareness of health-care providers and patients of the role of transplantation. The overwhelming majority of children and a significant majority of adults with SCD are covered by state Medicaid plans. Several commercial third-party insurers include BMT for SCD as a covered indication in their fully funded plans. However, approximately 60% of commercial insurance plans are self-insured (employers determine coverage), which can result in large variations in coverage. Participation in the health insurance exchanges is growing, which might be good news for SCD coverage. Some state Medicaid programs cover BMT for SCD, but many others do not specify whether SCD is covered or do not provide coverage. Medicare is "silent" on coverage for SCD, which essentially means that it does not cover BMT for this indication because it leaves coverage decisions to

contractors who deny coverage because of high costs. NMDP and ASBMT has submitted an application for reconsideration of the current national coverage determination to CMS to expand the scope of coverage for HSCT.

In 2015, the workgroup focused on increasing health-care provider and patient/parent awareness of BMT for SCD to increase referrals and use of BMT for eligible patients. The workgroup recommends education sessions at health-care provider conferences, publication of findings from clinical trials and analyses of CIBMTR data, and education/information sessions at patient/parent advocacy organization conferences. NMDP continues to provide education and outreach to patients and providers to increase awareness of HSCT as a treatment option for SCD.

Several trials of BMT in SCD are ongoing and others are in the planning stages. The workgroup hopes that this collective energy will continue to push the field forward and increase the appropriate use of BMT as a therapy for this disease. Some evidence indicates that this might be happening. The workgroup has issued two recommendations (recommendations 25 and 26 in the appendix).

Discussion

Dr. Hartzman commented that another barrier to BMT is insufficient funding for BMT. Dr. Kamani said that only about 10–20% of patients who could benefit from BMT are undergoing this procedure. Dr. Walters pointed out that BMT saves money in the long term compared to the lifelong costs of SCD. Dr. Giralt said that cost data are important. Complications of BMT add to its cost, so studies need to show that the procedure saves money and cures most patients with SCD. Furthermore, people with other diseases who could benefit from HSCT lack access to this procedure, so the issue is not confined to SCD. Two thirds of patients with acute leukemia only undergo HSCT after a second remission or beyond. An important barrier is the insufficient number of transplantation programs. Dr. Campbell remarked that studies have shown that the lifelong cost of SCD is almost $1 million. Because SCD is progressive, BMT should be done before children develop organ disease.

Dr. Wagner said that the Advancing Care for Exceptional Kids Act of 2015 would increase access for children by developing a national referral system that allows children to receive care in another state. The plans to overcome barriers of the workgroup are appropriate, but other barriers need to be overcome.

National Heart, Lung, and Blood Institute (NHLBI); National Cancer Institute (NCI); and National Institute of Allergy and Infectious Diseases (NIAID) Funding Priorities Related to HSCT

Nancy DiFronzo, Ph.D., Program Director, Transfusion Medicine and Cellular Therapeutics Branch, Division of Blood Diseases and Resources, NHLBI

HRSA and the National Institutes of Health (NIH) have complementary missions of improving public health, but each achieves its mission in different ways. HRSA advances health through health-care delivery, whereas NIH does so through research supported by its 27 institutes and centers. NCI, NIAID, and NHLBI are the largest NIH institutes.

The vast majority of the NIH budget supports investigator-initiated research. Any investigator can apply for one of these grants in response to a funding opportunity announcement.

NCI, NIAID, and NHLBI have investigator-initiated research portfolios on various aspects of HSCT that are consistent with their mission. NCI supports evaluations of drugs and immunotherapies, ways to reduce GVHD and GVL, comparisons of HSCT to chemotherapy, and cell therapies to prevent and treat relapse and to treat cancer in patients with HIV. NIAID sponsors research on HSCT for immunomediated diseases, several autoimmune disorders, primary immunodeficiency diseases, and cellular cures for HIV/AIDS. NHLBI research focuses on optimizing HSCT, using HSCT to cure nonmalignant blood diseases and bone marrow failure syndromes, developing novel cell products and gene therapies, and creating HSCT approaches for HIV/AIDS. These institutes support at least 100 grants related to HSCT.

The three institutes support clinical trials using different mechanisms. NCI uses R21 grants for pilot studies and R01 and P01 grants for phase 1 and 2 trials. NCI does not support investigator-initiated phase 3 trials, and it only supports phase 3 trials conducted by its National Clinical Trials Network. NIAID issues clinical trial planning grants (R34) and clinical trial implementation grants (U01). NHLBI supports clinical trial pilot studies through the R34 mechanism, phase 1 and phase 2 trials through R01 and program project grants, and multicenter phase 2 and phase 3 trials through R01 grants.

The institutes use a smaller part of their budgets for NIH-initiated research programs and resource programs. They use requests for applications to indicate the types of research they are seeking. NIH-initiated research programs that are relevant to HSCT include:

- CIBMTR, which supports research to facilitate critical observational studies in HSCT
- Rare Diseases Clinical Research Network, which is made up of multiple consortia, including the Primary Immune Deficiency Treatment Consortium and the Chronic GVHD Consortium
- Beyond HAART–Innovative Approaches to Cure HIV-1, which encourages innovative approaches to eliminate HIV-1, including cell therapies and novel gene-therapy approaches
- BMT CTN, a national network that evaluates promising HSCT therapies in multicenter studies to improve the safety and efficacy of HSCT to treat malignant and nonmalignant diseases and evaluate novel cell products

Dr. DiFronzo highlighted recent accomplishments of the BMT CTN, including 50 publications and 26 trials that have completed accrual. These trials have made it possible to show, for example, that using two cord blood units is not better than a single unit once a minimum cell dose is reached and that haploidentical transplants are effective for hematological malignancies.

NHLBI resource programs include the Biospecimens and Data Repositories Information Coordinating Center, Gene Therapy Resource Program, and Production Assistance for Cell Therapy. These three programs could be useful to the transplantation community.

NIH is now required to provide Congress with a 5-year scientific strategy. NIH is collecting input on this plan from the public and will submit it to Congress in December. The pending 21st Century Cures Act will require the 27 NIH institutes and centers to develop their own 5-year strategic plans that are linked to the NIH plan. NHLBI is engaged in a strategic visioning process to develop its strategic plan.

Discussion

Dr. Giralt suggested that the ACBSCT develop a recommendation that strongly encourages the Secretary to advise Congress of the importance of continued funding for the BMT CTN, which has done more to advance BMT than any other program in the last 15 years. Ending the network would have a devastating effect.

Dr. Wagner asked about support for clinical trials of complex cell therapies, which are costly. Dr. DiFronzo suggested that institutions doing these studies might need to rely on philanthropic support. When trials supported by philanthropy are successful, other funders will step in.

Dr. McCullough pointed out that the ACBSCT could not vote on Dr. Giralt's recommendation because a quorum was no longer present. However, the council could hold a virtual meeting in 3 months to hear a report from the new workgroup and act on Dr. Giralt's recommendation. The council members present expressed support for Dr. Giralt's recommendation.

Update on NMDP Activities Related to Payer Policies and Access

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

The Affordable Care Act has increased enrollment in Medicaid and the Children's Health Insurance Program by 22%, and 11 million peopled have enrolled in health exchange plans. Almost 17 million more Americans now have access to health insurance, including coverage for HSCT. The act eliminated preexisting coverage exclusions and annual and lifetime limits on the costs of care. The act has had a positive effect on transplant centers.

Most insurance plans cover blood and marrow transplantation, but Medicare has coverage limitations. In 2000, 57% of patients undergoing allogeneic HSCT were aged 65 or older; this proportion rose to 19% in 2014. Today, 25% of adults undergoing HSCT are Medicare beneficiaries, an increase from 5% in 2005, so Medicare controls access to HSCT. Medicare currently covers allogeneic HSCT for leukemia, aplastic anemia, severe combined immunodeficiency disorder, Wiskott-Aldrich syndrome, and MDS (as part of a coverage with evidence development decision). Since Medicare agreed to cover HSCT for MDS, the number of patients with MDS undergoing this procedure has risen steadily.

Medicare does not cover HSCT for leukemia and it is silent on all other indications. When Medicare does not mention an indication in a national coverage decision, local fiscal intermediaries make coverage decisions on a case-by-case basis or create their own policies. No fiscal intermediaries have created a coverage policy for HSCT. As a result, centers that do transplantation must hope that these procedures will be reimbursed.

NMDP has requested Medicare coverage for HSCT for SCD, lymphoma, myelofibrosis, and multiple myeloma. CMS is reviewing the expansion request for SCD and myelofibrosis and is likely to make a decision in November or December 2015. CMS will consider the remaining indications starting in 2016. Medicare might agree to cover some or all of the four indications. Alternatively, CMS might provide coverage with evidence development, coverage with evidence development for some of the indications and final coverage for the others, or decide not to cover some or all of the indications.

Medicaid has low reimbursement rates. For allogeneic transplantation, Medicaid pays $63,245. The average cost of a cell source is $40,000 to $45,000, leaving little money left to pay for all of the other costs of transplantation. Outpatient reimbursement for allogeneic and autogeneic transplantation is only $3,045.31, which does not cover any of the center's costs. NMDP has asked CMS several times to increase these reimbursement rates, but CMS has declined to do so. NMDP is therefore seeking a formal policy review and perhaps congressional action.

Public Comment

No public comments were offered.

Adjournment

Dr. McCullough adjourned the meeting at 4:34 p.m.

Appendix: ACBSCT Recommendations and Current Status

	Recommendation Summary	Status
1	That the Food and Drug Administration (FDA) finalize its draft guidance for industry on minimally manipulated, unrelated allogeneic placental/umbilical cord blood intended for hematopoietic reconstitution in patients with hematological malignancies.	*October 20, 2009*: The FDA issued its guidance and a draft guidance advising entities on filing an investigational new drug (IND) application to access unlicensed cord blood units (CBUs) when a suitable human leukocyte antigen (HLA) matched cord blood transplant is needed to treat a patient with a serious or life-threatening disease or condition and no satisfactory alternative treatment is available. *March 2014*: The FDA published revised guidance.
2	That the Secretary restore full funding of the Center for International Blood and Marrow Transplant Research (CIBMTR) research-focused cooperative agreement with the National Cancer Institute.	The National Institutes of Health (NIH) provided additional funding to support the CIBMTR's research-focused cooperative agreement, which was renewed on March 1, 2013, and will continue until February 28, 2018.
3	That the Secretary direct the Centers for Medicare & Medicaid Services (CMS) to develop an appropriate strategy for a national coverage determination on allogeneic stem cell transplantation as therapy for myelodysplastic syndromes (MDS) based on a recent review of the literature.	*August 4, 2010*: CMS issued a national coverage decision allowing Medicare coverage of allogeneic hematopoietic stem cell transplantation (HSCT) for the treatment of MDS when provided to Medicare beneficiaries enrolled in an approved clinical study. *December 15, 2010*: CMS approved a study submitted by the CIBMTR for Medicare patients with MDS as eligible for coverage with evidence development.
4	That the C.W. Bill Young Cell Transplantation Program implement policies that conform to several principles to protect the privacy and confidentiality of those donating umbilical CBUs to the program.	*FY 2010*: The Resources and Services Administration (HRSA) conducted a review and determined that its contracts' privacy and confidentiality requirements align with the principles identified by the ACBSCT.
5	That the Secretary recognize both the AABB and the Foundation for the Accreditation of Cellular Therapy (FACT) as accreditation organizations for the National Cord Blood Inventory (NCBI) program. The ACBSCT will review HRSA's experience with the accreditation organizations with meeting HRSA's specifications 3 years after the recognition decision by the Secretary.	*FY 2012*: HRSA signed a memorandum of understanding with AABB and FACT allowing the organizations to conduct cord blood bank assessments and determine whether the banks met HRSA-specific criteria.
6	That informed consent principles and standards for public cord blood banking be implemented.	*August 2009*: HRSA conducted a review and determined that its existing contract language complied with the ACBSCT's recommendation.
7	That an expert panel be convened to review and recommend clinical indications for which stem cell transplantation is covered by insurance plans.	At its May 5, 2010, meeting, an ACBSCT workgroup was charged with developing options. The blood stem cell community leveraged the work of the National Marrow Donor Program (NMDP) and participated in its Advisory Group on Financial Barriers to Transplantation to address inadequate transplant coverage. HRSA is actively involved in these efforts.

	Recommendation Summary	Status
8	That the Secretary mandate that Medicare and Medicaid cover patient participation in clinical trials involving HSCT.	HRSA and its contractor, the NMDP, continue to work with CMS on a case-by-case basis to provide model benefits language for clinical trials involving HSCT.
9	That cord blood collections be improved and increased.	HRSA reviewed this recommendation with public cord blood banks participating in the NCBI program, and the recommendation has been adopted where applicable. In addition, HRSA and NMDP have worked with the public cord blood bank community to identify ways to increase and improve cord blood collection.
10	That the Secretary recognize HSCT for generally accepted indications as a covered benefit for all federal programs for which the Secretary has appropriate responsibility and oversight.	HRSA and NMDP are working with the American Society for Blood and Marrow Transplantation to create a list of indications for transplantation that represent the current standard of care. This list will inform future discussions of potential changes to coverage by federal programs. NMDP, through its Advisory Group on Financial Barriers to Transplant, has developed model benefits language to share with public and private insurers and benefits managers. HRSA is actively involved in these efforts.
11	That Medicare reimburse for the acquisition of blood, bone marrow, and cord blood products for HSCT on a cost basis similar to reimbursement for graft acquisition in solid organ transplantation.	Discussions between HRSA and CMS are ongoing on this issue.
12	That the Secretary clarify that the expiration date can be placed on an attached label provided with the unit at the time of release to a transplant center for CBUs that cannot bear a full label.	Through the FDA licensure process, which has resulted in licensure for five HRSA-funded NCBI banks to date (starting in November 2011), the FDA has clarified its guidance on labeling to permit attachment of a tag disclosing the expiration date and other information.
13	That the Secretary work with the FDA to review requirements for licensure in light of concerns about the potential for licensure requirements to result in increased costs and decreased availability of public CBUs with the goal that the FDA urgently meet with applicant cord blood banks and representatives of transplant centers to share and resolve concerns regarding licensure.	The FDA has engaged in several ongoing outreach efforts to educate public cord blood banks about the licensure process, how to meet licensure requirements, and how to submit a biologics license application. *March 2014*: The FDA released guidance for industry and FDA staff: Investigational New Drug Applications for Minimally Manipulated, Unrelated Allogeneic Placental/Umbilical Cord Blood Intended for Hematopoietic and Immunologic Reconstitution in Patients with Disorders Affecting the Hematopoietic System.

	Recommendation Summary	Status
14	That models for remote collection of CBUs be allowed with only limited, scientifically justified safety precautions. Also, that the Secretary allow for CBU collection from routine deliveries without temperature or humidity monitoring of delivery rooms in hospitals approved by the appropriate bodies for hospital accreditation.	A pilot program assessed whether remote cord blood collections can be performed safely and efficiently. The results showed that remote cord blood collections (1) increase opportunities for expectant mothers who would not otherwise be able to donate their umbilical cord blood because there is no collection hospital in their area, (2) can be conducted safely and efficiently, and (3) increase awareness among racial and ethnically diverse populations.
15	That the Secretary recognize public cord blood bank oversight of the collection process as a sufficient means to ensure safe manufacturing practices and oppose the requirement for hospitals to register with the FDA as the establishments responsible for recovery.	*December 2011*: The FDA communicated that, in general, recovery establishments are required to register and list with the FDA (21 CFR Part 1271) unless an exception applies.
16	That the Secretary support the collection of cord blood from uncomplicated deliveries in accredited hospitals without environmental monitoring of delivery rooms.	*December 2011*: The FDA published its Guidance for Industry: Current Good Tissue Practice and Additional Requirements for Manufacturers of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps). This guidance provides information about environmental control and monitoring issues that should be considered for recovery of HCT/Ps.
17	That the FDA recognize and accept laboratory-developed testing (LDT) performed in Clinical Laboratory Improvement Act (CLIA)-certified, high-complexity, histocompatibility laboratories.	*September 30, 2014*: The FDA published its proposed LDT regulatory oversight framework, which is available for review and public comment. The FDA is seeking feedback on LDTs used for rare diseases and traditional LDTs interpreted by laboratory professionals who are appropriately qualified and trained as required by the CLIA regulations, among other issues.
18	That the FDA broaden the IND and biologics license application (BLA) clinical indications for unrelated donor cord blood transplantation to include use for hematopoietic and/or immune reconstitution or enzyme replacement in any situation where HSCT is the appropriate approach to treatment.	*November 2011*: The FDA granted the first license for a cord blood product, which is licensed for use in patients with disorders affecting the hematopoietic system. Subsequently licensed cord blood products have had similar indications.
19	That all cord blood products have the same IND and BLA clinical indications, which is scientifically and medically sound.	*March 2014*: The FDA revised its language for covered indications. The titles of both FDA guidance documents now correspond with each other: ("…intended for hematopoietic and immunologic reconstitution in patients with disorders affecting the hematopoietic system"), and thus they are "the same" per the recommendation.
20	That a transition plan, initially stated as on or before October 20, 2011, be implemented to allow time for the FDA to review recommendations 17 and 18 and to allow for institutional review board reviews of any changes needed.	The FDA continues to work with other sponsors to address the availability of cord blood products.

	Recommendation Summary	Status
21	That CBUs collected through the distribution of kits sent to motivated maternal donors or obstetrical units by an obstetric provider that meet all NCBI program and FDA qualifications be eligible for listing by the NCBI program and for FDA licensure.	*May 2011*: The FDA confirmed that public cord blood banks, including those with NCBI program contracts with HRSA, may apply for a BLA that covers remote kit collections. *May 2012*: The first NCBI cord blood bank submitted an application for cord blood collected through the distribution of kits. The FDA approved the collection model, and these units are eligible for NCBI program funding and listing.
22	That the Secretary take and support all reasonable efforts to ensure that compensation for marrow, peripheral blood stem cells, and similar products continues to be prohibited.	*October 2, 2013*: HRSA published a notice of public rule-making in the *Federal Register*. Responses are still under internal HRSA review.
23	That the Secretary consider appropriate mechanisms to ensure that the revised National Heart, Lung, and Blood Institute publication, "Management and Therapy of Sickle Cell Disease," include expert opinion about the curative option of HSCT for this disorder.	The ACBSCT's recommendation was shared with the National Heart, Lung, and Blood Institute by the National Institutes of Health ex-officio ACBSCT member. Some changes were made to the final publication that was released in 2014.
24	That HRSA undertake educational/outreach efforts to the sickle cell disease (SCD) patient and provider community to educate them about the progressive nature of SCD, increasing morbidity and mortality in early adulthood (ages 16–35 years), and role of HSCT and its complications.	HRSA is engaging in public and professional outreach at national and regional SCD conferences and is working to ensure that the appropriate audiences, including primary care physicians and hematologists, are reached.
25	That the Secretary recognize HSCT for SCD as a covered benefit for all federal programs for which the Secretary has appropriate responsibility and oversight.	*End of FY 2014*: The recommendation was under internal review at HRSA.
26	That the Secretary direct HRSA and other Department of Health and Human Services agencies to collaborate with the CIBMTR to review research-level data collection on allotransplants performed for SCD and consider appropriate reimbursement to optimize research data collection. This review should include SCD-specific data elements collected, completeness of data collection, and mechanisms for reimbursement.	The recommendation is under internal review by HRSA and its contractor.