ADVISORY COUNCIL ON BLOOD STEM CELL TRANSPLANTATION (ACBSCT)

U.S. Department of Health and Human Services (HHS)

Virtual Meeting

Thursday, May 29, 2014

Welcome and Opening Remarks

Edgar Milford Jr., MD, Chair, ACBSCT

Edgar Milford, Jr., MD, ACBSCT Chair, called the meeting to order at approximately 10:00 a.m. and welcomed all Council members as well as participants to the meeting.

Program Report

Shelley Grant, MHSA., Chief, Blood Stem Cell Transplantation Branch, Division of Transplantation (DoT), Health Resources and Services Administration (HRSA)

Ms. Grant reviewed the legislative authority for the C. W. Bill Young Cell Transplantation Program (the Program) and the National Cord Blood Inventory (NCBI). Both of these initiatives were authorized by the Stem Cell Therapeutic and Research Act of 2005, which was reauthorized in October 2010.

The goals of the C. W. Bill Young Cell Transplantation 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 program appropriations for fiscal year (FY) 2013 and 2014 were $21,877,000 and $22,154,000, respectively. The President's budget for the Program in 2015 is $22,109,000.

The NCBI provides funding to cord blood banks to collect, process, store, and make available high-quality, diverse umbilical cord blood units (CBU). It also aims to make cord blood units that are not appropriate for transplantation available for research. NCBI has as a target to collect at least 150,000 new units. NCBI appropriations for FY 2013 and 2014 were $11,147,000 and $11,238,000, respectively. The President's budget for the program in 2015 is $11,266,000.

Ms. Grant explained that the NBCI consists of high-quality CBUs collected by contractors representing thirteen accredited, public, cord blood banks. These thirteen banks are geographically dispersed across the United States. Some NCBI banks also make kits available to expectant mothers for remote collection capabilities. In addition, NCBI contractors collect cord blood units from approximately 110 birthing centers.

As of September 30, 2013 a total of 63,960 NCBI cord blood units were available. The funded target for FY 2013 was 79,592. Specific targets have also been set for ethnic and racial groups, and these targets were exceeded or almost met for each of these groups. In FY 2013 a total of 714 NCBI cord blood units were distributed for transplant. The same amount of units were distributed in FY 2012.

Ms. Grant provided an update on the C.W. Bill Young Cell Transplantation Program. As of September 30, 2013 (end of FY 2013), the Program's registry included approximately 11.2 million adult donors. More than 3.05 million of these (27 percent) self-identified as belonging to a racial/ethnic minority group. In FY 2013 a total of 397,584 adult donors were added to the program's registry. Of these, 205,607 (52 percent) self-identified as belonging to a racial/ethnic minority group.

The total number of cord blood units available through the program (both NCBI and non-NCBI) in FY 2013 exceeded 193,000. A total of 6,283 transplants were facilitated in FY 2013 (compared to 5,832 in FY 2012 – an increase of 7.7 percent). From a domestic standpoint, 4,866 transplants were facilitated in FY 2013 (compared to 4,427 in FY 2012 – an increase of 9.7 percent).

The total number of cord blood transplants – both NCBI and non-NCBI – was 1,102 in FY 2013 (compared to 1,191 in FY 2012 – a decrease of 7.4 percent). The number of cord blood units shipped – both NCBI and non-NCBI – in FY 2013 was 1,575 (compared to 1, 637 in FY 2012 – a decrease of 3.8 percent).

On October 2, 2013, a Notice of Proposed Rule Making was published. The purpose was to seek public comments on the proposed change in the definition of "human organ" in section 301 of the National Organ and Transplant Act of 1984, as amended, to explicitly incorporate hematopoietic stem cells within peripheral blood in the definition of "bone marrow."

This would clarify that the prohibition on transfers of human organs for valuable consideration applies to Hematopoietic Stem Cells (HSCs) regardless of whether they were recovered directly from bone marrow (by aspiration) or from peripheral blood (by apheresis). This amendment will also conform to section 301 of the Stem Cell Therapeutic and Research Act of 2005, as amended. The deadline for receipt of comments was December 2, 2013. A total of 533 comments were received.

Discussion

Dr. Price asked Ms. Grant if she knew what the gist of the 533 comments was.

Ms. Grant said she would ensure that the council would have access to the Federal Register link, as comments have been made public online. She added that the department had examined and analyzed the comments, but is not able to provide any specific details as the analysis is not publically available.

Lessons Learned Pre- and Post-Licensure

New York Blood Center
Andromachi Scaradavou, MD, National Cord Blood Program (NCBP)

Dr. Scaradavou's presentation discussed their experience with FDA licensure and the impact it had on their cord blood bank. Licensure required a steep learning curve. Staff had to review various documents to understand specific requirements and then find ways to comply with them. One example was stability studies. The bank had to develop laboratory validations of the effect of long-term cryostorage on cord blood products. The issue of stability is reflected on the product's expiration date, which has to be present on its label. Validation of stored cord blood products is performed annually. If the product meets all acceptance criteria, its expiration date can be extended for one year.

The bank held its first pre-BLA meeting in 2009 and submitted its BLA in January 2011. Various amendments had to be submitted following FDA requests resulting from teleconferences and letters.

Licensure required rigorous review as well as extensive validation of all processes, assays, controls, and materials. A considerable amount of time, monies, and commitment were needed to obtain licensure.

Dr. Scaradavou explained that of the 60,385 units currently in the NCBP search inventory, close to 5,000 have been licensed since November 2011. NCBP has distributed approximately 5,200 units for transplant since its inception. Of these, 65 are licensed products. She noted that as a result of changes related to costs and higher TNC at collection, their inventory is growing at a lower rate than before. The decreased growth affects primarily licensed products.

The increased banking costs have resulted in higher costs for cord blood products. Dr. Scaradavou explained that in 2008 the price for a cord blood unit was $35,000 while in 2012 the price for an IND unit was $42,000 and the price of HEMACORD unit was $45,000.

Dr. Scaradavou said that HRSA's reimbursement for NCBI units covers a fraction of the cost of the collection, manufacturing, and testing of the unit. Nevertheless, this represents an important revenue for banks. In fact, for most banks it is the only revenue other than the distribution of cord blood products for transplant. She added that increases in HRSA subsidies would significantly impact both future inventory and the sustainability of cord blood banks.

St. Louis Cord Blood Bank & Cellular Therapy Laboratory
Donna Regan, MT(ASCP)SBB, Director, SSM Cardinal Glennon Children's Medical Center

Ms. Regan described the various changes made by her organization to obtain licensure. The capital equipment costs and renovations that took place at their cord blood bank in preparation for the BLA included the establishment of a microbiology laboratory. They had previously sent samples for microbial surveillance to the diagnostic laboratory at their clinical institution, but the institution's lab did not have the resources or knowledge to pursue a validation of the rapid microbial method against that which is mandated.

They also renovated their clean space. This included installation of HEPA filtration, positive pressure, pass-through windows, etc. They implemented a rigid policy that included a rotation schedule of disinfection agents to keep microbial agents at bay and performed disinfection effectiveness studies.

Another change was the implementation of more robust monitoring of aseptic processing through the technique of observation, media films, and other processes to make sure that staff was compliant with aseptic techniques. The environmental modeling plan was improved to be much more comprehensive. They hired an independent housekeeping contractor to reach the GMP level they thought was necessary.

Both a quality unit and a quality control section were created. The quality unit includes a quality specialist who is responsible for approving or rejecting all products, reagents, procedures, etc. The quality control section is comprised of technical staff who are able to perform reagent conformance, equipment qualification, and facility maintenance.

Other changes included validations for collection processing and characterization; tighter documentation and timing controls and processing; upgrading of IT systems, and characterization of assays and instruments. In all, pre-licensure costs totaled $1.6 million dollars, while ongoing costs (e.g. staffing) are expected to reach $600,000 annually. The price on the sale of the unit in 2010 was $22,800 dollars but in October 2013 – after not increasing costs for six and a half years – the cost increased to $35,000.

Ms. Regan offered kudos to the FDA in being cautious and considered in regulating cord blood. She said the FDA had taken the needed time to formulate regulations to allow for flexibility, thereby recognizing the value and uniqueness of each product.

University of Colorado Cord Blood Bank
Brian Freed, PhD, Executive Director, ClinImmune Labs

Dr. Freed explained that the University of Colorado Blood Bank is an independent and relatively small bank. It became licensed in 2012 and since then has transplanted 700 units in 25 countries.

It began working on a GMP facility in 2005 when the bank was moved out of the University of Colorado Hospital and into a biotech park. A clean room was taken over at that location and renovated. In all, costs to obtain licensure were approximately $900,000. Ongoing annual costs are close to $200,000. Dr. Freed explained that cord blood banking:

- Requires a significant investment in cGMP facilities and protocols
- Is labor-intensive, in part due to the need for monitoring batch records
- Requires significant informatics support
- Requires highly-trained regulatory oversight

Dr. Freed explained that under the current system they are banking a lot of inventory, of which 90 percent might potentially never be used for transplants. As cords are collected and come into the lab, they have an average TNC count of approximately 1×10^9, but the units that are transplanted are on average significantly larger.

Dr. Freed showed data from a transplant physician who transplants about 25 to 30 cord blood units a year. The physician uses cord blood as a primary source of transplants, even over matched unrelated donors. Over a two year period, the average TNC for this physician was 1.6×10^9 for HLA-A, B and DRB1 match, with a 6 out of 6 match. For a 5 out of 6 match the average was 2.1×10^9 and with a 4 out of 6 match the average was 2.8×10^9.

Data also show that small cord blood units remain in inventory much longer. Transplanted units of a TNC of less than 1×10^9 are released – on average – after 10 years, while units larger than 2×10^9 are released – on average – after 2.5 years. Dr. Freed said there is a tremendous amount of expense associated with banking and storing because most of the units are smaller. They may be part of an inventory, but they are not part of the effective inventory.

He believes that if HRSA were to reconsider its TNC cutoff – even though it would be more expensive per unit to do so – it would be more cost efficient for banks because they would not be spending more money to store and maintain units that may not be used.

Carolinas Cord Blood Bank
Joanne Kurtzberg, MD

Dr. Kurtzberg discussed the impact of FDA licensure on cord blood banking and transplantation at the Carolinas Cord Blood Bank. She said that as an academic center, Duke had never before held a BLA and therefore did not have a full understanding of the necessary facility requirements. Changes needed to obtain licensure included upgrading their quality systems unit by increasing personnel from two to seven staff; developing an electronic document control system; and finalizing stability protocols. In 2013 they underwent a one-year post-licensure review which resulted in additional changes.

In terms of a timeline, they held a pre-BLA meeting with the FDA in 2010 and received licensure in 2012. One-time costs for licensure were approximately $5 million, which included $3.2 million for facility renovation. Ongoing yearly costs reached $1.5 million. These included hiring new staff; cleaning, engineering, and operations; and increased documentation.

The bank has added approximately 4,000 licensed units over the past two years. The bank's overall rate of adding eligible units to the inventory has actually decreased due to increased expenses. They had to close two of their long-standing collection sites as costs did not allow keeping all sites open.

Dr. Kurtzberg said her bank examined NMDP data to better understand the collection and banking characteristics of both domestic and international cords. Data show that current post-processing TNC cutoff at the bank is 90 X 10^7 with a current rate of discard of 70 percent of registered donors (or 55 percent of collected units). The majority of inventory is comprised of units that have a TNC cutoff of less than 125 x 10^7 (post- processing) while the majority of units chosen for transplant have a cutoff larger than 175 x 10^7. If the bank chose to increase its cutoff to more than 175 x 10^7 it would have to discard 92 percent of collections.

Dr. Kurtzberg also presented modeling results of how increasing the TNC cutoff threshold would impact African American cord blood units. She explained that at the current qualifying post-TNC cutoff of 0.9 x 10^9 the bank would need more than four times the number of African American cord blood units with measured post-TNC to have an equivalent rate of discard to Caucasian cord blood units.

Dr. Kurtzberg concluded her presentation with the following recommendations:

- Increase HRSA reimbursement or find alternative sources of funding for units that are costing more to manufacture
- Do not require requalification of FDA-approved reagents and supplies for human use
- Increase the "nimbleness" of the system to allow for minor changes in processes, reagents, and supplies (e.g. creation of a simple algorithm for mild changes)
- Address the issue of lower sales and increased costs
- Continue to address potency and stability
- Upgrade IT systems used to analyze outcomes data

LifeCord Cord Blood Bank

John Wingard, MD, Medical Director, LifeCord Cord Blood Bank

Dr. Wingard said he represents LifeCord, a relatively small cord blood bank. It has about 7,000 units listed in inventory. LifeCord collects from nine hospitals in Florida, Georgia, and Alabama and is in the process of collecting from two additional hospitals in Miami and Birmingham.

When LifeCord was faced with the challenge of licensure, it was financially in the red as it has been over the past 12 years of its existence. Significant changes were required. Prior to licensure, LifeCord had a cooperative venture with the hospital transplant stem cell laboratory. All cords were processed in the laboratory using good tissue practices, which is the conventional practice in transplant cell processing laboratories.

However, it later became clear that, although the FDA stated that they did not require a GMP facility, it would be practically impossible to meet FDA requirements in a consistent manner with the current stem cell laboratory processing methods. After multiple conversations with the FDA, LifeCord decided to construct the GMP facility which led to an outlay of more than $600,000.

LifeCord also invested another $400,000 in necessary consultants, trainings, and purchasing of new equipment. An additional $141,000 was also incurred in the preparation for submitting a BLA. These costs were related to performance validation, monitoring, testing materials, etc. With respect to staffing, two additional FTEs were required which resulted in an additional staffing cost of more than $90,000 per annum. All these costs resulted in a 20 percent increase in the cost per unit. In order to recover its capital outlays, LifeCord increased the price per unit by 25 percent. These costs, along with other opportunity costs, were a big challenge to LifeCord.

Dr. Wingard said that, both as a transplant clinician and a transplant director, he was not sure that they had improved the product offered to their clients – the transplant community and patients. Also, he believes it is uncertain as to whether they have truly added quality. In addition, the organization is now competing with banks that have not met licensure requirements and [are offering products at] a lower cost. He added that it is not clear for many of their clients that the latter are inferior products, so they do not have a competitive edge. Dr. Wingard said that as a result of this there is no guarantee from a financial perspective that licensure has added value. He added that from a quality standpoint there are also serious reservations.

Discussion

Dr. Milford asked if there are any differences between a licensed and an IND unit when a transplant center searches for a cord blood unit, other than the objective criteria for unit selection. He also asked what proportion of the transplants are done now – and are projected to be done – with IND vs. licensed units. In addition, what role do international units play in the mix?

Dr. Scaradavou replied that about 10 percent of their recent distribution had been licensed units, so for two-and-a-half years about 10 percent of their units have been licensed. She added that from her point of view as a banker and a transplant physician, the benefits of licensure have not always been appreciated on the transplant physician side. Physicians still select units based on TNC and HLA match, while the issue of the quality usually comes third. There are incoming studies that highlight the fact that TNC is not the best indicator and that quality has to become a priority. Currently, only a small note on the unit indicates that it is licensed, but it is not clear how much validity this has for transplant centers. There are many units being imported into the U.S. This reflects the diverse population of patients and the fact that physicians are trying to match patients as best as they can. Some of the units from abroad have gone through a set of very different – but rigid – criteria of approval while others have not, so it is a mixed group.

Jeffrey R. Schriber, MD, said that as a transplant physician he first looks at size. They also look at how well they are matched, but not so much as to whether it is a licensed product. All things being equal, they do look at where the units come from because there are track records and some places are more reliable than others in terms of numbers. Dr. Schriber also said that although cost does come into play – and cost is indeed a factor – if one has the best unit in terms of size and match, that still will be used because keeping the patient alive and doing better is the most important factor. Dr. Schriber said that during their presentations the centers at St. Louis and New York said their numbers had actually gone down in terms of distribution. He asked if this was the case for everyone.

A participant agreed that numbers are indeed down. Part of the reason is because there are more banks spread over a larger area worldwide.

Dr. Milford recalled that Dr. Boo gave a presentation a while back this year that showed that national cord blood use is down, and this was made up for – to some degree – by increasing the use of haploidenticals.

Naynesh R. Kamani, MD, said that transplanters generally go for the largest units with the best match to the recipient. He asked how one could demonstrate, with good scientific data, that licensed units in fact make a difference in terms of outcomes for recipients?

Dr. Kurtzberg agreed and said that as a banker and a transplanter she does not think that licensure has actually increased the quality of the units. More is done and documented, and one can prove a lot more about environmental monitoring, but she said she looked at their pre-licensure contamination and engraftment rates and they seem similar to their post-licensure rates. She added that because there has been growth in the inventory, there has also been more HLA diversity which makes it possible, in many cases, to get better matches. This, however, has nothing to do with licensure.

Dr. Milford asked if all units processed have to be under licensure if a bank has approval to license products. Also, are there banks that are still collecting new units which are not licensed, but under IND? In other words, is there an ability to mix things up?

Dr. Kurtzberg said that there is indeed an ability to mix things up. First, all licensed banks have legacy inventories that predate their licensure and which they are still distributing. This makes up the vast majority of the inventory available for transplantation today. There just are not enough licensed units to be able to switch to exclusive distribution of licensed units, nor should there ever be a reason to do that, because the legacy units have been proven – for nearly twenty years now – to be capable of engraftment and conferring hematopoietic reconstitution. Second, even in licensed environments there are some exclusions from licensure. For example, her bank would accept certain types of units under IND, such as those under travel exclusions or units where the donor has screened positive for the hepatitis B core antibody but their confirmatory test is negative, their NAT test is negative, and their surface antigen is negative. She said she would still bank and distribute such units under an IND although it is not eligible for licensure. So it is all mixed up.

Dr. Milford asked what would be the benefit for a cord blood bank to be licensed.

Dr. Freed said it is not so much about benefits but that there might not be a choice in the future. It is not clear when this could happen, but the FDA might require licensure in the future. He added that quality banking has being going on for a long time so on average the products were good. As a result of FDA licensure, however, fewer fringe products will be seen, such as those that might be too old. Fewer such units will sneak through, even though this was a small percentage anyway. However, it is unlikely that this will be reflected in the statistics, such as engraftment or survival rates.

Mark C. Walters, MD, said that Dr. Kurtzberg and Dr. Freed observed that smaller size units appear to be underutilized and retained for a longer period of time. What are some ideas about the disposition of these units in the future?

Dr. Kurtzberg said there might be more use of these units in the future due to new technologies being developed for hematopoietic reconstitution as well as other applications in regenerative medicine such as tissue repair and regeneration (e.g. cardiovascular injury, type 1diabetes, and hypoxic brain injury in younger children). There are emerging technologies where these smaller units may be good source material for the generation of other products.

Dr. Freed said they have shipped units to Colleen Delaney for expansion, but even in expansion trials she said she would prefer bigger units. He said his feeling was that, as far as clinical trial go, they will always want bigger. Dr. Wingard agreed.

A participant said that licensure cannot improve the quality of the unit. What it can do is to avoid mixing a unit into the licensed category that increases risk through the procedures. He added that even though the percent of severe adverse events is very low overall, it is still a problem and licensure ought to take care of this.

Dr. Kurtzberg said she disagreed with the previous comment. In many cases the incidence of severe adverse events are related to issues that have nothing to do with licensure.

Dr. Milford said they have received units that are thawed and do not have good viability. It is not clear what happened or where it came from, but in the licensure world this type of issue is less likely to occur.

Dr. Scaradavou said the point is control of processes and consistency. Rather than thinking that one IND unit is better than one licensed unit, one should think about products as a whole.

Dr. Schriber asked if there was a mechanism to somehow quantify this. He said they have had the experience where a unit says it has a certain number of cells but when it is tested the count is lower. Dr. Schriber also noted that speakers showed that licensure is very expensive but that individuals may not always know that it is valuable. He gave myeloma as an example. CD34 cells can be purged, but no one does it anymore because it is clinically irrelevant. He asked if what is currently being done is something that is very expensive, looks very nice, but is clinically irrelevant. If that is the case, should this still be done or is there another mechanism to capture its value?

A participant said they are currently accumulating data from the CIBMTR, so eventually there will be enough data to make a comparison between licensed and IND units, but it will take time. Overall, with respect to engraftment and the big picture, he believes there will probably only be a marginal effect. However, one also needs to consider that the FDA may not consider [unlicensed units] as an option in the future.

Dr. Schriber said that if it turns out to be an incredibly expensive process without a foreseeable benefit, it could raise the question as to whether there is a need for licensing. It may be more useful to say something like “our minimal target should be higher” which would be a viable and useful approach based on the data presented.

Dr.Kurtzberg said she had asked the FDA what it would take to undo the licensure requirement and the FDA replied that it would take new legislation stating that it is no longer required. The participant added that accreditation standards are fairly well aligned with most of FDA guidelines – except for facility requirements, environmental monitoring requirements, and QSU requirements where FDA standards are more rigorous. If there is some reconciliation with accreditation, which might be happening, the question then becomes “Does one need both licensure and accreditation?” There are some emerging data showing that units transplanted from accredited banks appear to have better clinical outcomes as compared to units from non-accredited banks. The other question is whether cord blood licensure will lead to FDA requiring other stem cell products to be licensed. For example, currently there is discussion about mobilized peripheral blood having to be licensed. This raises some concern because with mobilized blood the product is already directed to the patient and there are certain rigidities in the way that SOPs are managed and viewed by the FDA that may be impossible to implement in the collection of mobilized blood. The impact of this could be cost prohibitive, resource prohibitive, and not feasible.

Dr. Price said the issue is not so much that the FDA is requiring licensure, but the specific licensure requirements. Blood products have to be licensed but getting them licensed is not as complicated. Also, some individuals believe that the FDA is requiring them to do some things that banks believe are a bit silly, such as revalidating reagents which are already approved. He added that the expense comes from

the fact that the bar has been raised so much. If it was more similar to existing blood rules, licensure could be a lot less expensive.

Dr. Milford said he recalled that in the early days there was resistance by those involved in bone marrow transplantation to have the regulations be under the blood rules. Unfortunately this backfired and it is now under manufacturing rules.

Ms. Regan said that an unintended consequence could be the stifling of innovation and change. If one has to put in a submission every time one changes a hematology analyzer or a new technology is on board, it may be difficult for others to invest in it because it can take months to get it through the FDA. The message sent to corporate partners, as well as device manufacturers, is that change is too hard. Change is already hard enough but if one has to move forward with validations and qualifications in the approval process that consumes significant resources and time, it might discourage some from moving forward.

Dr. Milford asked how many new *collections* have gone under IND by all banks as opposed to licensed banks in 2014.

Dr. Freed said they are essentially no longer doing INDs as HRSA will no longer reimburse for IND units.

Dr. Scaradavou's said that in New York they do about 15 percent, and this has to do primarily with donor eligibility. For licensed units one needs eligible donors. One could accept units from mothers that have traveled or lived in Europe and considered them as an IND. If a lot of those units are eliminated, one risks minority donors.

Dr. Wingard said the majority of cord blood banks that list units with the NMDP are not licensed. Therefore, the majority of the new cords that are added to the registry are not licensed because there are only five licensed banks out of nearly two dozen.

A participant said that 50 to 70 percent of the banks are still not licensed for the reasons that Ms. Regan and Dr. Scaradavou explained.

Dr. Wingard explained that the comments shared today are just from the banks that have been licensed and are experienced with licensing, but he suspects one might get a different perspective from bank directors that have not yet been licensed. He added that both existing units, as well units being collected today, are in the first case grossly in favor of IND units and in the second case the majority of IND units. Therefore the intent of the FDA in the future might have a big effect on the availability and cost of units for those banks that are not the five licensed banks discussed today.

A participant added that if most of those banks are in fragile financial basis, and the financial impact is going to play a huge role, the question is whether they will continue in operation or close down. Some banks might continue as IND banks indefinitely. However, it would an unfair footing if some banks are be able to continue as IND banks.

Dr. Wingard said this is indeed a concern. He said their bank spent a significant amount money to obtain licensure, but they are hearing from physicians that they are going after the number of cells, rather than whether the unit is licensed or not. From a business perspective this is a disadvantage.

Jeffrey McCullough, MD, said they published a study about ten years ago that looked at 250 units shipped to the University of Minnesota for transplantation. They applied their quality system to those units and found various quality issues, some of which very minor (such as the mother having traveled to a

malarious area) and others very concerning (such as units being shipped for transplant without transmissible disease testing being completed). He added that they just finished a similar, but larger, study for all units up to 2013 which showed almost the same number of quality issues. The study does not distinguish between licensed and unlicensed products, but it does suggest that if one looks at quality issues they way they did, there has not been a lot of progress in the last eight or nine years. However, the study may also suggest that due to licensure a very large number of these "quality" issues were minor and would not impact the likelihood of a successful transplant or the safety of the unit. An example would be "six months before delivery the donor took a vacation in Mexico." So one of the things one might want to discuss is whether there are aspects of the current licensing system that have no real effect on the quality and safety of the unit and whether that might be streamlined in order to reduce the cost and burden of licensure.

Dr. Milford suggested that members of the council mull over the comments and decide whether there are issues that the council should address, or have a subgroup address.

Update on NMDP Activities Related to the Affordable Care Act

Michael Boo, JD, Chief Strategy Officer, Administration and Business Development, NMDP
Stephanie Farnia, MPH, NMDP

Dr. Boo began his presentation by providing a brief background on the Affordable Care Act (ACA) which became law in 2010. He reviewed some of the impacts of ACA implementation with respect to transplants.

The "Essential Health Benefits Set" forms the core of what must be met by any insurance provided under the ACA. It requires coverage of several high-level care categories. Bone Marrow Transplants (BMT) and other transplants are not specifically defined, although components of BMT are indeed covered. As a result, the ACBSCT developed the following recommendation in 2010:

"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."

Dr. Boo said that a survey of providers showed that BMT is sometimes explicitly provided but too often it is provided implicitly. He said it is important that the Secretary address this issue with clarity when she takes it up in 2015. At that time there will be an assessment as to whether the products in the Exchanges fully provide the coverage intended by law. It is hoped that there will be a recommendation by the Secretary clarifying coverage.

Another goal of the ACA is to reduce costs. Some of the mechanisms to reduce costs include limiting networks, potentially limiting coverage, and changing reimbursement. Limiting networks may result in a transplant center not being considered "in-network." For example, in the Twin Cities area 13 plans are offered, but only nine have an allogeneic stem cell transplant program "in-network." It is not clear how limited network issues will be handled. For example, if a patient needs a transplant in a limited network plan would that be done in a single-case basis or would that patient be faced with "out-of-network" costs to access a program? Also, will the patient's access to transplant programs be limited? In other words, will that patient have to go to the closest center when another one may be a better fit because it specializes in their disease?

The Leukemia & Lymphoma Society sponsored a study of four states to determine if National Cancer Centers were included in the Exchange products. Their survey found a significant lack of access to National Cancer Centers in the states surveyed. This suggests that patients may have access to

transplants, but it may not be of the highest quality for their specific disease. Dr. Boo explained that network adequacy and "out-of-network" options will receive more scrutiny from HHS in future.

Dr. Boo said that one area of success is increased Medicare coverage for MDS patients that may benefit from transplants, In 2010, only five patients had their transplants covered by Medicare, while in 2013 a total of 274 patients received coverage.

In 2010, the ACBSCT made the following recommendation in regarding Medicare reimbursement:

"ACBSCT recommends to the Secretary that Medicare reimburse for the acquisition of blood, marrow, and cord blood products for hematopoietic transplantation on a cost basis similar to how reimbursement is made for graft acquisition in solid organ transplantation."

The NMDP followed-up with Medicare on this specific issue. In December 2013, NMDP and ASBMT partnered and met with CMS staff to request pass-through of acquisition costs on a "Reasonable Cost Basis." This is the same model used for solid organ transplants. CMS indicated that they would review and consider the request. However, CMS has not yet responded.

Dr. Boo said the topic for their 2014 Forum is to define quality and value in SCT. The forum aims to address various key questions including:

- How do we define value for SCT?
- What outcome measures matter most to clinicians?
- What quality metrics are most useful to purchasers?
- How do we incentivize great care without penalizing?
- Can payers align on quality and value measures?

Dr. Boo concluded his presentation by discussing their efforts in working with transplant centers to improve cell source cost reporting. One of the goals is to show that the Medicare reimbursement formulas do not adequately provide appropriate coverage. The goal is to reach 95 percent reporting by 2016.

Discussion

A participant said that one of the slides presented showed that the vast majority of allotransplants, about 80 to 85 percent, were from nonexempt places. The participant said their bank is nonexempt and they get about $40,000 to $50,000 in reimbursement for an allotransplant. They effectively lose money on these. Also, this does not include costs for finding a donor. The costs for searching a donor are often borne by either the patient or the center. This severely impacts access. The participant asked if it would be worthwhile for the council to resend the 2010 recommendation, as they appear not to have been acted upon. Would it be helpful to have the Secretary say she agrees with the recommendation and perhaps put pressure on CMS?

Dr. Boo replied that the reimbursement figures quoted were accurate. The autologous reimbursement is somewhere around $40,000 and the allogeneic reimbursement is around $50,000. This includes acquisition of the cell product. Clearly, transplant centers are subsidizing medicare populations, which is one of the most rapidly growing segments for transplantation. He said they would be happy to bring back a recommendation to the group for consideration at the November meeting.

Dr. Milford agreed it would be useful to have an update.

Action Item
Dr. Boo agreed to bring back a recommendation to the group for consideration at the November meeting.

Dr. Kamani asked how Dr. Boo's payor group would be able to influence Medicaid quality. Dr. Kamani said that Medicaid programs are state funded and sometimes follow CMS policies, but not always. Therefore, how can Dr. Boo's group influence decisions made by Medicaid insurers?

Dr. Boo replied that Medicaid is subject to state regulations so there are variations in terms of benefit definitions. The ACA is intended to bring coverage into some uniformity, but half of the states have not adopted those rules. There are both policy issues – whether there should be standardization of coverage elements across the country, as well as the level of reimbursement. Dr. Boo said they are reviewing this on a state-by-state basis but are doing it somewhat reactively because resources are limited and the focus is on the federal side, the Medicare side.

Dr. Milford said there is a global concern with Medicaid coverage in general, not just the application discussed. There is also the fact that states feel they are legally responsible for deciding the scope of coverage for any range of medical conditions. Dr. Milford said that perhaps something can be done to try to [apply] pressure, but at the state level as the federal government is not in the business of dictating to states about coverage and cost issues.

Dr. Kamani said he mentioned this because most of the recipients of transplants for sickle cell disease are Medicaid insured.

Advancement in Cellular Therapies — Workgroup Charge/Accomplishments/Next Steps
Claudio Anasetti, MD, Chair

Dr. Anasetti said the CIBMTR has provided updates to the Advisory Council on Blood Stem Cell Transplantation (ACBSCT) regarding its efforts with collecting outcomes data from entities involving infusion of blood cells from a donor that are outside of the traditional scope of cell transplantation for hematopoietic reconstitution. In May 2012, the CIBMTR asked ACBSCT members to provide assistance in reviewing the scope of Public Law 109-192, as authorized in 2005, and as amended through reauthorization in 2010, as Public Law 111-264.

In response to this request, Dr. Milford established a workgroup of Cellular Therapies during the May 2012 ACBSCT meeting to assess the work scope of the Stem Cell Therapeutics Outcomes Database, as required by the HRSA contract with the CIBMTR.

Since approximately 2010 Drs. Rizzo and Pasquini have provided an update of CIBMTR efforts to capture and report on data from emerging cellular therapies for alternative applications involving a donor. CIBMTR has also established a sub-workgroup to identify best practices for capturing data from procedures that are not aimed at hematopoietic reconstitution, created forms, and established data collection time frames and information technology systems that would enable capturing information on a voluntary basis from organizations outside of its traditional scope.

The CIBMTR has encountered some challenges and opportunities including the following:

- Most cellular therapy activities are performed under the cover of intellectual property or commercial sponsors and therefore investigators are not willing or able to share data
- Despite comprehensive efforts, the response to data collection was low

- To date, outcomes data have been collected from approximately 400 cases, mainly from 6 different transplant centers. But 94 percent of the data come from only one center. Therefore, the present data registry may not be representative of the broader cellular therapy field.
- There is an opportunity, however, because the CIBMTR has received a grant to explore cellular therapy data collection.

Dr. Anasetti also provided a review of relevant HRSA efforts. HRSA asked the office of General Counsel to review the legislation as it is specified in the public law for what concerns collection of data. HRSA's Office of General Counsel specified that HRSA has the latitude to define by the Secretary what is in the best interest of patients regarding the capturing of data for the SCTOD contractor. However, HRSA has limited availability of resources for broad data collection.

HRSA's position is that it would be in the best interest of the legislation and the patients that it serves to continue capturing data on outcomes of blood stem cell transplantation and other cellular therapy activities that involve a donor (i.e., volunteer adult donors and umbilical cord blood units that it facilities through the C.W. Bill Young Cell Transplantation Program and its National Cord Blood Inventory contractors. The scope would include cellular therapy beyond the traditional indication of cellular therapy for the purpose of hematopoietic reconstitution.

Dr. Anasetti said he believes that the Council would be left with very little space, or even no room, for recommendation. As a result, the ACBSCT may determine that data from cellular therapies from sources outside the C.W. Bill Young Transplantation Program and National Cord Blood Inventory contractors for purposes other than hematopoietic reconstitution may be captured by the CIBMTR on a voluntary basis.

Discussion

Dr. Kamani asked Dr. Anasetti if it was his interpretation of HRSA's position that HRSA would only have a question over blood stem cell?[inaudible] products used for allogeneic transplantations. He added that the majority of products used are autologous

Dr. Anasetti explained that the transplants that stem cell transplantation outcomes database (SCTOD) governs do not include the use of stem cells from autologous sources, whereas the allogeneic use of volunteer donors stem cells, cells, or cord blood in NCBI repositories are within HRSA's purview.

Dr. Walters asked if Dr. Anasetti had considered the blossoming area of genomic editing in the ?[inaudible] stem cell and then reinfusion along with the safety and efficacy issues related to that application. He asked whether he thought there is a role for the council to weigh in on that area of research.

Dr. Anasetti said there have been discussions about the blossoming area of gene modification of cellular therapeutics and there is extreme interest from all parties in being on top of this and collecting data from trials conducted using cells that come from the adult donor [inaudible] registry or cord blood banks. If there is a need for agencies other than the FDA to collect data on activities outside the purview of the C. W. Bill Young Cell Transplantation Program, then there would be the need for additional resources to be allocated through legislation or other mechanisms. He added that they would be interested in a broad view and a detailed report of current activities in gene or cellular therapy that are going on using other types of cells.

Dr. Price asked the following question: If a bank sells a cord to someone who is exploring a neurologic application, whether the cord is suitable for transplant or not, – would it be included on what HRSA thinks it needs to follow? If so, does anybody know of a mechanism that is working for such cases?

Dr. Anasetti said his understanding was that HRSA would be interested in collecting data if NCBI cords are used, for example, for regenerative medicine or neurological disease. However, cords from other sources that are used for those indications would not be within the program.

Dr. Price asked whether it would have to be a cord that went through all the processes, got banked, and then got listed as NCBI.

Dr. Anasetti said he thinks that is correct.

Dr. Milford said he believed it would include any unit distributed through the C. W. Bill Young Cell Transplantation Program ? [inaudible] which the NMDP collects data on. He said he had forms to follow-up on units that are not used for hematopoietic reconstitution.

Dr. Price said he believes that units sold to researchers are likely not the ones that have been banked as part of the HRSA program.

Richard E. Champlin, MD, said that about half of the units that they collect are not big enough to be useful for transplantation. Those are the ones that are prioritized for research purposes.

Dr. Milford said he recalled a presentation by CIBMTR that showed they had a mechanism in place for units that were distributed through the program – even if they were used for nonhematopoietic reconstitution – to have follow-up on those units. However, this would not include units that are not part of the program.

Dr. Kurtzberg said their transplant center does use autologous units for treatment of babies with brain injuries. They often receive units from other private cord blood banks. CIBMTR takes reporting on both autologous and allogeneic products that are part of NCBI or are bone morrow or mobilized blood or mesenchymal stem cells that are not part of the specific program but are infusions of cellular products to patients in the U.S. Whether it is NMDP-facilitated, part of NCBI, or a totally different product from industry, it can be reported through CIBMTR on the cell therapy form. Cell therapies such as T-cell vaccines, or DLI, and other types of infusions may also be reported. Dr. Kurtzberg said she believes that this type of activity should continue to be reported to the CIBMTR. She added that HRSA's position is reasonable and should be respected. The issue is whether the council should recommend that HRSA include in their contracts that CIBMTR, or the contractor, continue to collect these data.

Dr. Douglas Rizzo, the project director for the stem cell therapeutic outcomes database SCTOD, explained that they do in fact have a mechanism to collect cellular infusions outside the usual perspective of cellular therapies such as infusions for hematopoietic cell reconstitution, subsequent T-cell infusions, or mesenchymal stem cells that are performed in the setting of a traditional hematopoietic stem cell transplantation. Data systems collect this information routinely and regularly. These systems have also been adapted to collect other therapeutic indications and uses of those cells. One should be cautious, however, about setting expectations of the C.W. Bill Young program in areas of alternative indications for cellular infusions. He explained that CIBMTR has tried to appeal to stakeholder groups – such as those involved in neurologic regeneration, cardiac regeneration, and other indications – for several years. Although many in the field believe that value can be brought to those communities (in terms of organizing and reporting on the data, analyzing the data, etc.) it is not clear to the stakeholders that it represents value, especially when there is no reimbursement or other resources to assist with data reporting and when they are involved in IND or other proprietary activities that might be seen as threatened, whether or not it actually happens.

Thomas H. Price, MD, asked if they are collecting data on the infusion as well as neurologic outcome data.

Dr. Rizzo said that at the moment they are only collecting survey data. The goal is to understand what is happening, therefore, the data being collected are the indication, the types of cells infused, and other pre-infusion data. He added that their systems could be adapted to collect those data so it is not really about system capability. The issue is to determine the incentive or requirement for centers to report those data, and then build the scientific expertise in outreach to those communities with their interested and engaged involvement to define what those relevant outcomes should be so that the correct forms and data systems can be designed to collect relevant and appropriate outcomes that those communities believe are important and wish to report.

Dr. Milford said he believes the biggest issue is a severe acquisition bias in the absence of a global, mandatory charge for anybody doing this kind of work to report it and to have the appropriate resources to collect the necessary information. Right now it is voluntary and many organizations are doing it under proprietary small systems. It may not be the right time for mandated data collection.

Advancing Hematopoietic Stem Cell Transplantation for Hemoglobinopathies — Update
Naynesh Kamani, MD, Chair

Dr. Kamani reviewed the workgroup's two-fold charge which is to:

- Identify barriers to transplantation and opportunities to more fully realize its potential for individuals with sickle cell disease and thalassemia
- Submit for consideration and adoption by ACBSCT recommendations regarding high priority actions

The workgroup held a conference call in early March 2014. The topics discussed centered around the NHLBI publication and how to ensure that the provider and patient community were adequately and appropriately informed. Dr. Kamani also reviewed the recommendation made by the Council on May 2013:

"The Council recommends that the Secretary consider appropriate mechanisms to ensure that the revised NHLBI publication management and therapy of sickle cell disease includes expert opinions for this disorder."

In response to this recommendation, the group was informed by NHLBI that it had reviewed the guidelines, although they have not yet been published and will not cover the role of HCT in sickle cell disease in any detail. NHLBI also made some minor changes to the guidelines. However, the group felt those changes would not result in a publication that would inform the provider and patient community about the appropriate role and indications for bone marrow transplantation and sickle cell disease.

During the last conference call, the workgroup also discussed other options to disseminate the message about the curative potential of hematopoietic cell transplantation in sickle cell disease. The group decided that it would consider approaching the *Blood Journal* to write a "Perspectives" article that would inform health care providers about evidence-based recommendations for the use of hematopoietic cell transplantation in the management of sickle cell disease. The group is still in the process of discussing this item. The workgroup also discussed a recommendation made to the Advisory Council on Blood Stem Cell Transplantation. Dr. Kamani also discussed the educational and outreach efforts carried out by NMDP towards the patient and provider community.

Dr. Kamani reviewed the status of various clinical trials for bone marrow transplant in sickle cell disease. Trials are underway and preliminary results for at least one trial should be available within the next 12 months. He also reviewed CIBMTR data showing that bone marrow transplantation for sickle cell disease is being used more frequently now than ever before. In the last year cycle reported a total of 187 transplants were recorded. This is not a total number, as cases continue to be reported. Still, this therapeutic approach continues to be vastly underutilized for a variety of reasons. Dr. Kamani also showed data that showed that the number of bone marrow transplants for thalassemia have been relatively steady over the past 15 to 20 years with anywhere from 200 to 300 transplants reported annually.

Dr. Kamani explained that the workgroup would like to continue to address the following items over the next year or so: 1) Continue discussion on either the "Perspectives" article or a white paper on the appropriate role of HCT in sickle cell disease; and 2) Continue to address issues related to access.

Discussion

Dr. Price asked Dr. Kamani what would be an appropriate number of annual transplants in his opinion.

Dr. Kamani said it would be difficult to come up with an appropriate number. He said that of the nearly 100,000 patients with sickle cell disease, approximately 10 to 25 percent have the severe form of the disease. Conservatively speaking, if 10 percent of the patients would be eligible for transplantation by virtue of having the severe form of the disease, the estimate would be in the several thousands, although only a few hundred are currently being transplanted. He added that this does not take into account the well-known relentless progression of the disease during the lifetime of the patient, especially during the late teenage years and in early adulthood. That group is excluded from the calculations. Instead, he is referring to, for example, children with sickle cell disease.

Dr. Walters said that one would think that about 1 percent of the population might need access annually, but this hinges on whether transplants are used as an experimental therapy or as a standard therapeutic option for affected individuals and their families. The sickle cell disease guidelines are an important issue and one that they plan to address directly through the article they are considering writing. The impression one gets from the guidelines is that it is an experimental therapy. This would continue to limit, for a number of reasons, access to this type of care.

Cord Blood Thawing and Washing — Workgroup Charge/Accomplishments/Next Steps
Jeffrey McCullough, MD, Chair

Dr. McCullough explained that preparation for cryopreservation and the actual cryopreservation constitute important steps in cord blood banking. While banks provide thawing and preparation instructions to transplant centers, many centers may not be adequately prepared for cord blood processing and infusion. Another challenge is that preparation, thawing, washing, and transfusion procedures vary among transplant centers. Also, transplant centers may use the bank's thawing and washing recommendations inconsistently or the center's staff may not be formally trained in the necessary procedures.

To address these and other challenges, the workgroup suggested a series of actions including to:

- Determine whether there is a clinical effect on different pre-cryopreservation procedures
- Reduce the number of different thawing protocols at the transplant center laboratory
- Create a training program for cord blood thawing and washing
- Require transplant centers to validate the thawing procedure in use

- Formalize guidelines for single and double cord blood infusion
- Ask accrediting agencies to create relevant standards for cord blood processing at transplant centers
- Require transplant centers to train staff on thawing/washing techniques
- Reduce the number of different thawing protocols
- Publish a white paper on cord blood thawing and infusion
- Work with NMDP, CIBMTR, and BMT CTN to strengthen thawing/washing processes and training
- Request AABB and FACT to enhance inspection related to thawing/washing and transfusion
- Consider a randomized trial comparing thawing-only vs. washing
- Develop recommendations for transplant center activities
- Urge/support the development of an enhanced adverse event reporting system

Dr. McCullough also provided details of a current CIBMTR study on the clinical effect of cord blood processing. He described various NMDP, CIBMTR, and BMT CTN activities and their progress to date. In addition, Dr. McCullough reviewed the following resolution from a previous Council meeting:

"The workgroup proposes that the Council recommend to HRSA that the following descriptions of activities that occur at the transplant center laboratory be used by the cord blood coordinating center as a blueprint to develop additional training, technical assistance, or operating policies."

Dr. McCullough said the workgroup also held a number of conversations with Dr. Warkentin and Ms. Loper to determine how the inspection process and standards could be better harmonized. He explained that at the last meeting they also discussed the adverse reporting system developed by NMDP. The system seems to be in place and functioning.

Discussion

Dr. Champlin said that one way to think about this is whether there is a center-specific difference in rates of graft failure or slow engraftment. In other words, are there problems in handling and thawing cells that would result in cell damage and that would be reflected by a higher rate of graft failure and/or time to engraftment? Looking at such data could provide some insight as to whether there really is a problem.

Donna Regan, MT (ASCP), SBB, said there really are no center-specific data available to do this. It was a review paper with both published data and some other data from the authors' centers.

Dr. Champlin said there are transplant-center data from the stem cell therapeutic outcomes database on the engraftment of every patient post-transplant. If the transplant center laboratory is handling the thawing of the cells, then that center might well have a problem with a higher rate of graft failure with cord blood transplants and a longer time to recovery than other centers.

Ms. Regan said the level of detail to glean some of that information is only available in an adverse event report to the NMDP, so the denominator is pretty small. It is work in progress.

Dr. Kurtzberg said there is also another component of adverse reaction which is infusion reaction.

Dr. Milford asked whether there is a big difference in the so-called "package inserts" about what the post-processing procedures should be. He also asked Dr. McCullough if other than the wash/no-wash option there are other major manipulations done to a unit which might differ among centers once it arrives and before/during the infusion process.

Dr. McCullough said he believes there are three fundamental approaches: 1) Thawing the unit and infusing it directly; 2) Thawing the unit [and applying] a dilution process developed by Dr. Rubinstein; or 3) Washing the unit, which implies dilution and removal of supernatant while adding more suspension. He added that there are other kinds of problems that might arise; for example, thawing done at the bedside or done by a remote laboratory which could result in a substantial interval of time before the thawed cells are infused. That could also be applied to cells processed by other methods – how soon they are infused and how they are handled between preparation and infusion.

Dr. Kurtzberg said that a lot of the devil is in the details. For example, the dilution can be done at a 1:1 or 1:8 ratio and the level of dilution matters for the viability of the cells. Also, when one dilutes for a very small child, the product cannot be administered without washing and concentrating the volume. There are also issues around ABO compatibility. One of the reasons there may be more reactions with red cell containing units is that in the early days of cord blood transplantation, people said that ABO did not matter. However, incompatible red cells still cause intolerance if they are infused in a large enough volume. Time is also important. There have been instances of units that were thawed and then sat on a bench or were transported for up to five hours. There is also the issue of the unit being infused in a time period that is too short for the size of the patient and the volume of the infusion. All of these things may influence whether or not the patient has an infusion reaction. Some of these issues might also impact the viability of the cells in the unit before transplantation. One needs to consider all of these different details. With respect to Dr. Milford's initial question, cord blood banks do have detailed instructions and everyone sends a protocol, although some protocols provide various options while others are very specific. Licensed banks do have to include thawing instructions as part of their package insert. However, more often than not, transplant centers do not follow them. There is also no obligation to follow them. As a result, practices are varied, validation is sporadic, and knowledge about the nuances that impact the patient's safety and product liability are not as generalized as they ought to be.

A participant said that one of the challenges in trying to address this involves accreditation organizations, their standards, and their inspection process. NMDP could be an ideal source for training and education. Also, if there are data to be collected, it would make sense that CIBMTR be the group that collects it. However, the issue has not been framed in a cohesive approach and it is not yet clear whether some organizations share the concern that it is a substantial enough problem to merit effort.

A participant said she was torn by the following question "Should one follow a specific procedure assessed by the cord blood bank or should one have center-specific thawing procedures that are optimized by the center and carried out every time with units from different banks?" She added that maybe having a validated procedure should be something that is built into the AABB accreditation process.

Phyllis Warkentin, MD, said it might be better to think about standards, requirements, and accreditation as one thing, because if it is in the standards and the requirements, then it should be inspected against. She added that they began to take an interim report from each transplant center that had not been inspected and which required the wash and dilute procedures about a year ago, when the standard first came into effect. If they were not inspected under those standards, then they were asked to submit their procedures. Currently, 40 programs have submitted such procedures, which are highly variable and – in general – reflect a poor understanding of why the procedures are being done. More centers are more concerned about DMSO content than they are about red cell. There are a few programs that did not submit anything and others that believed that it was a "pretty silly standard that should not be kept in the standards for the next edition." There is some sentiment in the reports that people do not necessarily believe it is a huge problem. Dr. Warkentin said they are putting forth the effort to ensure that people are following the standards and that they have come into compliance with the new standards.

A participant asked if she had a sense, from reviewing those data, about the extent to which the laboratories had validated whatever procedure they were using.

Dr. Warkentin said there are some outstanding places that provided examples of five or more practice units of various types to validate their procedures. However, these are in the minority. Most problematic are laboratories that at most only use one, two, or three units a year. Some places informed them that they are "going to do whatever they tell us because we don't do enough to validate the procedure." It is important to keep in mind that sometimes procedures will vary in the smallest detail, or they may have a reagent included in the wash solution that the laboratory does not readily have available or cannot find. Also, some international banks have sent recipes that have something that U.S. banks do not have.

Dr. Warkentin said she believes more effort needs to come from the clinical end. Clinicians have to understand what they are doing, why they are doing it, and what needs to be ordered because the laboratory does not necessarily feel empowered "so to speak" to write the order for how to process the particular product. Often the labs depend on the clinicians to write the order. So, education about these issues could be expanded to ASBMT.

A participant said that perhaps they should try to have an educational session at the ASBMT meeting because it stands to reason that the goal is to retain as many stem cells in cord blood units and not lose them during the thawing process, so the patient can attain the best recovery possible.

Dr. Warkentin agreed it would be a great idea.

Kathy Loper, MHS, MT (ASCP), senior director of cellular therapies for AABB, said that AABB standards also require validation and staff training competencies for all processes – including thawing of such products. She said they have seen similar issues to those described by Dr. Warkentin. There is no standard method and a medical director is usually more comfortable using his or her own method. As a result, the manufacturer's instructions may not be followed. Also, since there is a lack of good peer-reviewed reference material in the literature, the paper submitted by Dr. McCullough will be very helpful. She added that most standard setting organizations might not set very specific instructions for how to thaw a product because it might differ, for example, based on whether the cord blood will be expanded vs. transplanted in its entirety. Ms. Loper agreed with Dr. Warkentin that more effort is needed from clinicians and that there is a need for standardization in the field. She said that if the standard setting organizations – at least from the AABB perspective – had a specific request about whether AABB could add a certain component, that they could certainly consider it.

A participant asked whether the information AABB has is confidential, as it was obtained through its inspection process. He added that if there was a way to put this information together it could provide a nice picture of what is going on.

Ms. Loper replied that the assessment process includes reviewing the thawing procedure, equipment, staff training, way it is done, etc. However, that information is neither brought back to AABB nor captured in a database. Instead, it is reviewed in the context of "Do the procedures and policies in place at the facility meet the standard?"

A participant said they do have that kind of information because they have specifically asked for it. Programs that submit an annual report have been specifically asked to send their procedures for thawing and/or diluting and/or washing units at the time of transplant. The participant said that while they would not be able to share what specific program the information came from, they could certainly tally it without identifying a specific program. Tallies could be developed of whether labs choose to always dilute, choose not to dilute, choose to wash, etc.

Dr. McCullough said this would be very helpful.

A participant said that with adult stem cells there was a rush of ensuing depletions. The participant asked what other kinds of treatments were taking place before infusing the cord blood unit into the patient.

Dr. Kurtzberg replied that there are about five or six main techniques currently being tested at sponsored clinical trials. One is notch technology, which the Fred Hutchinson Cancer Research Center is using. Initially they were forming double cord transplants and taking one of the cords and then thawing it and expanding it] and then infusing it on the same day as the un-manipulated cord. The Center is also part of an NIH trial that is also a double cord transplant, but instead it is expanding cords, cryopreserving them, and then using them as third parties to augment engraftments without HLA matching. Another technology developed involves cells that are expanded for 21 days in a cocktail of growth factors and then harvested and infused. This was done initially along with the second unmanipulated cord and is now also being done with a single cord transplant. Another organization is exploring the incubation of cords. The cord is first thawed, then incubated for about two hours with a compound, and then washed and infused. A similar approach is being tested at the MD Anderson Cancer Center. There is also another protocol at the MD Anderson Cancer Center were cords are being thawed and expanded on mesenchymal stem cells for a few weeks prior to infusion. There is yet another protocol that includes CD26 stimulation and involves incubation, infusion, and then treatment of the patient with drugs before and after engraftment.

A participant said that most of the organizations involved in the trials described above are on the sophisticated end of cell processing. She added that what is being discussed at this meeting is more basic information (e.g. washing) and probably affects programs that do not do too many cord blood infusions.

Dr. Kurtzberg agreed.

Dr. Rizzo suggested some next steps. Dr. Warkentin could summarize what they know about the different processing mechanisms. Perhaps Dr. Rizzo, Dr. Kurtzberg, and Ms. Regan could begin some discussions with NMDP to gauge their interest and determine whether there may be ways to explore some training programs, or sessions, through NMDP. Another step would be for anyone who sees Miriam A. Markowitz (AABB) to put some pressure on to get the manuscript out. A final step would be discussing the possibility of getting something on the agenda for the next ASBMT meeting. He asked if Dr. Champlin would be the right person to do this.

Dr. Champlin replied that he is not on the organizing committee but could certainly carry the message.

> **Action Item**
> Dr. Warkentin will summarize information on the different processing mechanisms. Dr. Rizzo, Dr. Kurtzberg, and Ms. Regan will begin discussions with NMDP on the possibility of training sessions through NMDP. Dr. Champlin will discuss the possibility of getting the topic on the agenda at the next ASBMT meeting.

Status Report — Realizing the Potential of Cord Blood and Scientific Factors that Make a Unit High Quality — Workgroup Charge/Accomplishments/Next Steps

Thomas Price, MD, Chair, Realizing the Potential of Cord Blood
Joanne Kurtzberg, MD, Chair, Scientific Factors that Make a Unit High Quality

Drs. Price and Kurtzberg provided an update on two workgroups: 1) the Realizing the Potential of Cord Blood workgroup; and 2) the Scientific Factors that Make a Unit High Quality workgroup.

The initial charge of the Realizing the Potential of Cord Blood workgroup was to identify important gaps and strategic opportunities with regard to more fully realizing the potential of cord blood in such areas as clinical research, technology development, and the economics of public cord blood banking. At least initially, the group was to focus on the cord blood role in transplantation for hematopoietic reconstitution. This basic charge was actually fulfilled and a presentation was given to the ACBSCT in May 2012 on the group's findings. Some cord blood economic issues still remain, but these were mostly switched to HRSA. At the time the workgroup did not recommend that the TNC threshold be increased.

The other workgroup, Scientific Factors Necessary to Define a Cord Blood Unit as High Quality, had as an aim to define a high-quality cord blood unit. A variety of issues were addressed and resolved including: exclusion rules; clarifying cell count requirements; kit modeling; synchronizing accreditation requirements between HRSA and NCBI criteria; expiration dates and stability; standardization of CBU release criteria; determining the minimum donor age; and overwrap requirement.

During the group's last conference call, held in March 2014, the group heard a presentation from Dr. Boo on cord blood usage trends. The key point was that the use of cord blood seems to be trending down (about 10 percent down in 2013). At this time it is uncertain why this is occurring. Another issue discussed was the cord bank economic issue, which is now in HRSA's court. Finally, there was a proposal to merge the two workgroups.

Three recommendations were made to the Council. The first was to merge the two workgroups due to significant overlap in discussion items and members. The second recommendation was that the committee's charge be revisited – the group will continue to evaluate the characteristics of a high-quality cord blood unit and revisit the recommended minimum TNC threshold. The third recommendation was to expand the group's charge to include considerations other than hematopoietic reconstitution (e.g. use of cord blood in graft engineering, immunotherapy, etc.) and the use of cord blood in regenerative medicine.

Discussion

Dr. Milford said one of the suggested items for discussion, "The characteristics of a high quality cord blood unit," is relevant as a HRSA deliverable. However, there is an also global issue regarding high-quality that does not have to [meet] HRSA's characteristics (i.e. what is fundable).

Ms. Grant agreed and added that discussion of the TNC threshold might also help guide them in terms of what is reimbursable or permissible.

Dr. Price asked Ms. Grant whether, in terms of the deliverable, if HRSA has a deadline for getting back to Congress?

Ms. Grant said there might not be a deadline for this particular purpose. HRSA would suggest that the Council evaluate, for example, the Memorandum of Understanding held with the various accrediting organizations before moving forward and informing Congress. The areas of high-quality cord blood units, characteristics, and looking at TNC are areas that HRSA will continue to monitor on an ongoing basis. The Council's review and feedback on these areas would be helpful.

Dr. Kurtzberg said there might be some time sensitive issues to discuss because the legislation will be up for reauthorization in 2015. If there is a need to change wording in the legislation regarding what is a high-quality unit to enable HRSA to contract differently, then it should be discussed. This might relate to pricing per unit, how many units are banked per year, quotas, etc.

Dr. Price asked what the group thought about the idea of expanding the scope to include considerations other than hematopoietic reconstitution. If the scope were to be expanded, what would be the charge for the use of cord blood in graft engineering, regenerative medicine, immunotherapy, etc?

Ms. Grant said one could consider looking at best practices for collection of outcome data.

Dr. Price asked if the charge would be basically the same as the original charge, except to reevaluate it with respect to scope (looking at clinical research, technology and development, etc.).

Ms. Grant agreed this would work from the perspective of HRSA, but said she would defer to the Chair.

Dr. Milford said the question is really about deliverables. What would be the end product of such a deliberation? One could have, for example, a regular time-limited report on what the workgroup considers to be the characteristics of a high-quality cord blood unit for the purposes of HRSA and reimbursement.

Dr. Kurtzberg said the quality issue could be resolved by going through prior committee work as well as FDA regulations and existing standards and taking on the two pieces: 1) testing and potency; and 2) the TNC threshold. The latter is more business than quality. Modeling around the reimbursement issue could be discussed and addressed by the committee, although it is not a quality issue.

Dr. Milford agreed and said that modeling might be necessary because the issue is not going to be "black and white." There will be a curve of positive and negative aspects that have to be balanced against one another. There will also be a set point at which one gets maximum benefit.

Dr. Price said they had spent a lot of time on this from the business perspective with a lot of input from NMDP and Mr. Boo and his group. They developed spreadsheets on the optimal TNC from a business perspective. The spreadsheet could be updated, but one might still have to consider whether it would be strictly business or [other factors may need to be considered so as to], for example, not miss valuable minority cords that may not make the threshold.

Dr. Milford said that models do exist to make such a determination. It is a matter of decision analysis.

Dr. Price asked if the decision would be to make a recommendation to HRSA and then at that point HRSA could decide whether to adopt it or not.

Ms. Grant said they could make a recommendation to HRSA or a recommendation to the field. As previously mentioned, the criteria that HRSA sets is regarding the minimum reimbursement but others have noted that they have an inventory of units that are at a certain TNC and that those smaller units are not necessarily being used.

Dr. Milford agreed with Ms. Grant. If the audience is the transplant clinician, or the transplant center making a decision about what to do, most individuals would use the biggest unit they can, but that is different from the question "What is reimbursable at the level of the cord blood bank?"

Dr. Price said the transplant clinician may want the bank to keep every unit, so that the clinician may later locate a suitable cord that would not have been there had it not been banked in the first place. However, the cord blood bank has a different perspective – the business perspective. Dr. Price said he believes that cord blood banks may elect to have a much higher TNC than HRSA is reimbursing just for that reason. Different arguments might come into play.

Dr. Kurtzberg said that if the TNC cutoff is set at a level where only 10 percent of units are banked, one should also consider having clear messaging for the public. If such a decision is made one should be very transparent about it with donors. Donors get very enthusiastic about donating. Even though they know their unit may not actually qualify, they have expectations that it will.

Dr. Milford asked how many of the units are reimbursed by HRSA.

Dr. Kurtzberg said that if one uses the current HRSA cutoff as the minimum threshold, which is 900 million cells post-processing, then it would be about 42 percent.

Dr. Milford said there was general consensus about the committee charges, and that the group could wordsmith them later on.

Action Item
The workgroups will be merged and its charge will be revised.

Dr. Milford asked if Dr. Rizzo could comment on Dr. McCullough's manuscript.

Dr. Rizzo said the manuscript and the analyses were presented to the Thaw and Wash Workgroup by Dr. Eapen and Dr. Ballen in February. There was a review of the analyses and the manuscript which resulted in a request for additional data to be reviewed.. Additional data were incorporated and the manuscript is expected to be recirculated to interested parties within the next two weeks. The manuscript incorporates methods for processing grafts at the cord blood bank prior to freezing. It also discusses a few manipulations that may occur at the level of the transplant center, including the method of thawing and washing or diluting at a macro level. The time period between the thaw and the infusion is also discussed in the manuscript. The numbers are not large, so there may be a future opportunity after a few more years of accumulating information to revisit the analyses. The target submission date for the manuscript is the end of June.

Dr. Milford asked to what degree CIBMTR is collecting information – and to what level of granularity – about processing at the transplant center.

Dr. Rizzo said they collect data at two levels. In terms of what happens at the level of the transplant center, they collect data on their Transplant Essential Data (TED) level forms and on an infusion form. The infusion [data] should be collected for all cord blood transplants and that includes details about how the unit was thawed, whether or not it was washed, any additives that occurred, etc. They also collect information on engraftment.

CCR5 and Transplantation
Willis Navarro, MD, NMDP

Dr. Navarro's presentation focused on a new protocol. He provided a brief overview on HIV and its mechanism of action. HIV typically uses the chemokine receptor CCR5 to enter cells and perpetuate infection. No existing antiretroviral therapies (ARVT) are able to clear the HIV virus completely. While some active regimens can halt the progression of the disease and stop viral replication for standard testing, there remains a latency of the virus within certain reservoirs. This has been one of the major challenges to finding a cure.

Naturally occurring variants of the CCR5 molecule exist. There are mutations which effectively make the CCR5 truncated and ineffective to HIV. This natural mutation occurs more frequently in northern Europe, although there are a few other European hotspots where the mutation is found.

In a *New England Journal of Medicine* article, Gero Hütter and his colleagues presented the case of a 40-year-old American man that lived in Germany and was diagnosed with AML. He had been previously diagnosed with HIV and was on ARVT with good results. He underwent a transplant using a CCR5Δ32 donor identified with homozygosity. The patient stopped ARVT during introductory chemo and was later found to have an expected rebound in his HIV viral load.

The load decreased after he went back on ARVT. However, after the transplant and being off ARVT no viral load burst or increase was seen. He has been off ARVT since the second transplant and has an undetectable viral load. The patient has remained in remission for more than five years. The study demonstrated that such transplants can not only be tolerated in the HIV setting, but that CCR5Δ32 might effectively convey HIV resistance. Although few patients with hematologic malignancies will have a similar donor available, the study's proof-of-concept is extremely valuable.

A protocol was developed with the experience of this patient in mind. The goal is to, first and foremost, show that it is safe to perform allogeneic transplants in the HIV setting. It is a small two-year study (n=15) is supported by the BMT CTN. The BMT CTN was created in 2001 and is supported by NHLBI, NIH, and NCI funds. The BMT CTN is a group of 20 core clinical centers with projects managed by a data correlating center.

The primary objective of protocol 0903 is to determine the 100 day non-relapse mortality. Secondary objectives include disease status, engraftment, complication rates, immune reconstitution, and HIV reservoir estimation. To be eligible, patients must be infected with HIV and have AML, ALL, MDS, or lymphoma and a match to a related or unrelated donor. To date 11 patients have been enrolled. Eight of them have been transplanted and two did not go forward to transplant. No CCR5Δ32 donors have been identified.

The identification of CCR5Δ32 donors has proved to be more challenging than initially anticipated. Also, the process requires time. This can be problematic because many of the patients have diseases that are fast evolving such as AML or ALL. Nonetheless, being able to replicate the proof-of-concept can help to understand if the CCR5Δ32 approach is a viable method to confer HIV resistance.

Discussion

Dr. Kamani asked Dr. Navarro if he could comment on the work done by Dr. Larry Petz who looked at their inventory of cord blood units to identify cord blood units that were homozygous CCR5Δ32.

Dr. Navarro said that Dr. Petz and others have taken on an important project to prospectively identify cord blood units that are CCR5Δ32 homozygous. In that effort, they have identified approximately 200 units with that feature. One of the challenges is that those units would have to match a patient. Other groups around the world have performed transplants using at least two of those units. One transplant was in Utrecht and the other in Spain. In both cases the approach was to do a haploidentical plus cord, with the idea that the haploidentical would temporarily provide a bridge of cellular reconstitution until the single cord, which had the CCR5 feature, would be available to kick in and possibly confer HIV resistance. The patient in Utrecht died from transplant-related complications before day 100. Unfortunately for the patient in Spain, the CCR5Δ32 homozygous unit selected turned out not to be a viable unit and as a result they had to move on to a different unit. Dr. Navarro explained that at this time the 0903 protocol does not permit the use of cord blood because the study's primary goal is to show the safety of allogeneic transplants in the HIV setting.

New Business

Dr. Milford asked if there was any new business.

Dr. Kurtzberg suggested that the Council make a recommendation to defer FDA consideration of licensure for mobilized peripheral blood transplants at the current time. She also suggested that the Council consider appointing a working group to examine the feasibility and impact of licensure and study the matter over the next year. Dr. Kurtzberg said she believed there had been communication between the FDA and the NMDP about the possibility of requiring licensure for PBSC transplantation. There is concern among the community of what that would mean and how it would be implemented. Some individuals feel that there should be some formal hold while the impact is more fully evaluated.

Dr. Milford asked if Ellen Lazarus, MD, Captain, USPHS could comment on the status of FDA's deliberations on peripheral blood stem cells.

Dr. Lazarus explained that there are currently no IND and BLA requirements for unrelated donor peripheral blood stem cells. There is, however, a voluntary IND and the NMDP has made that information publically available. The FDA recognizes the differences in the models of production, distribution, and use of cord blood compared to PBSCs. This is why there is no program in place that is similar to the cord blood program. She added that the FDA continues to appreciate the work that NMDP and HRSA are doing to develop programs where data can be obtained and which individuals in academic and regulatory settings can use to try to determine what the best practices are and the best ways to realize those practices. Dr. Lazarus added that any action the FDA takes to promulgate new regulatory programs would be done in a very transparent manner. The FDA would not engage in any private discussions or discussions with only one sponsor about developing licensure requirements.

Hearing no other new business, he opened the floor for public comment.

Public Comment Period

Dr. Milford asked the operator to open the phone lines for public comment and invited any member of public to identify themselves and their institutional affiliation, if any.

Via chat, Ms. Frances Verter asked Dr. Kamani if he knew what percentage of sickle cell patients in the U.S. are on Medicaid health insurance.

Dr. Kamani said they do not have an accurate percentage assessment. However, as a general rule the number of patients with sickle cell disease who are on Medicaid – whether they are children or adults – is comparatively higher than the population of patients with other diseases.

Hearing no other individuals with public comments, Dr. Milford closed the public comment period.

Adjournment

Dr. Milford adjourned the meeting at approximately 3:15 p.m.