Advisory Council on Blood Stem Cell Transplantation (ACBSCT)

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

Georgetown Hotel and Conference Center
Washington, DC
May 9, 2012

Welcome and Opening Remarks

Edgar Milford, Jr., MD, ACBSCT Chair, called the meeting to order at 8:10 a.m. and welcomed Council members and meeting participants. He expressed thanks to members leaving the Council and noted that new Council members will attend the next meeting. A list of meeting attendees is included as Attachment 2.

Program Update

Shelley Grant, MHSA, Division of Transplantation

Ms. Grant said she had no action for Council members to consider. She presented appropriations levels for Fiscal Years (FY) 2011 and 2012 for the C.W. Bill Young Cell Transplantation Program and National Cord Blood Inventory (NCBI), and the proposed levels in the president's FY 2013 budget. Ms. Grant noted that funding levels for FY 2013 are the same as those for FY 2012, indicating that dollars are being used very well. The FY 2013 budget has not been finalized.

Existing infrastructure contracts for the C.W. Bill Young Cell Transplantation Program end in FY 2012, and there is full and open competition for those contracts. A pre-solicitation notice was posted on FedBizOpps, www.fbo.gov, on April 15.

Ambitious goals are being developed for the transplantation program for FY 2014 through FY 2020. These goals are likely to emphasize annualized growth in total transplants, annualized growth in the size of the registry and the increased rate of patient survival at one year, post transplant.

Realizing the Potential of Cord Blood: Work Group Report

Liana Harvath, PhD, Work Group Chair

Dr. Harvath provided an overview and update of the Work Group's activities and noted there were no recommendations for the Council's consideration. The Work Group has focused on the cord blood role in transplantation for hematopoietic reconstitution, which is its charge.

Since the November 2011 Council meeting, the Work Group held one conference call, in March 2012, during which Steve Spellman presented and discussed the study "Impact of Matching at NIMA on Outcomes after 5/6 or 4/6 Mismatched UCBT for Malignant Hematological Diseases."

The Work Group suggested the following question move forward as a pilot project: "Can non-inherited maternal antigen (NIMA) typing be examined and considered prospectively

when selecting cord blood grafts?" Steve Spellman will present the topic to the National Marrow Donor Program's (NMDP) Cord Blood Committee's upcoming meeting.

Dr. Harvath reported that the Work Group has completed its primary charge of identifying important gaps and opportunities in clinical research, technology development and economics of public cord blood banking. A summary status report that includes three recommendations and their status is included in Council meeting attendees' folders. The group had a total of 14 conference calls since it convened on June 7, 2010: eight of the 14 calls focused on economic issues.

The Work Group did not make a recommendation to change the current lower limit of 90 x 10^7 TNC (total nucleated cell count) because members did not have sufficient information. The group is waiting for data on:

- Which groups receive the lower TNC cord blood units (CBUs)
- Whether the lower TNC CBUs are transplanted in African American patients because of rare human leukocyte antigen (HLA) types
- Whether the lower TNC CBUs achieve the best HLA match for the recipients

While the Work Group is technically sunsetting, Dr. Harvath suggested that it could be revived to address future issues as needed. She acknowledged Bob Baitty, who retired from government, for everything he has done for the community.

NMDP Update
Michael Boo, JD, Strategic Development Officer, NMDP
Mr. Boo said no Council action is requested.

Mr. Boo presented a HRSA Registry Models report that looked at how registry size analysis might be useful in answering the question of how to move ahead with identifying appropriate cord blood targets, in terms of number of units banked, ethnic diversity, etc. Twenty one different ethnicities within the U.S. population were identified in the analysis.

The report presented to HRSA concluded that there are four approaches to improving matched rate based availability for patients:

- Adult donor recruitment (continuing to add to adult donor recruitment is needed to keep this registry fresh and continue to improve its diversity)
- CBU "recruitment" (adding more cord blood to the inventory also has a strong impact on access)
  Mr. Boo said the question arises as to whether to target larger units to ensure access to more adults. The analysis indicates a strategy to add larger units would improve access for more adults. He said whether this proves true across all ethnic groups is something now being studied and that data will be provided shortly.
- Adult donor retention/availability (making the existing registry more effective)
- Improved transplantation outcomes with mismatched adult donors and/or smaller CBUs – i.e., clinical research

Targeting larger units would improve access to adults but it is uncertain whether that would cut across all ethnic groups.

Next steps for registry size analysis require looking at:

- Multi-race donors: model for one haplotype from one population and one haplotype from a second population
- Multiple cord transplants and their impact on this availability issue: the match rates, considering dose, allowing for two cords or three cords to be infused at once
- Cord Matching at C locus: are we at the same level of registry access that we think we are?

Discussion
Richard Champlin, MD, said increasing the size of the cord blood bank pool of donors will increase the chances of finding a good donor. Trying to do better in mismatches remains our big challenge in transplant, and it has been hard to improve the treatment-related mortality and complications we get with increasing mismatch. Therefore, finding a matched donor is still our best strategy if we could do it, and increasing the size of the cord blood bank pool of units clearly is desirable.

Dr. Milford asked Mr. Boo what his sense of the practice across the country is in different transplant centers in terms of what kind of donors they will accept for a patient. For instance, if someone needs a stem cell transplant, will the decision about whether there is an appropriate donor be different depending on where they happen to be sitting?

Mr. Boo said that, yes, different transplant centers have different protocols in terms of their selection criteria. Some will not accept a mismatched adult donor, others will accept one, some will accept two, some will have a protocol that includes cord blood if they cannot find an adult donor, and they have different cutoffs in terms of the dosage versus the mismatch. He said he sees variations across transplant centers in terms of protocols they use for selection based on their own research interests, comfort level and experience.

Bertram Lubin, MD, said that whether third party payers would pay depends on the donor source because there are variations in each state: this should be a factor in thinking about these issues.

Summary of Study, Relationship of Race/Ethnicity and Survival after Single Umbilical Cord Blood Transplantation for Adults and Children with Leukemia and Myelodysplastic Syndromes
J. Douglas Rizzo, MD, MS, Center for International Blood and Marrow Transplant Research (CIBMTR)
There were no actions or recommendations for the Council.

Dr. Rizzo said several people were part of the writing committee for the study he was presenting. Karen Ballen, MD, was the principal investigator for the study, which was to investigate the relationship between race, ethnicity and survival after single umbilical cord transplantation. The principal question she sought to answer was whether results of

transplantation using umbilical cord blood (UCB) are similar in Whites, Blacks and Asians. Little data exists to characterize the possible disparity in transplantation using UCB.

The study concluded that:

- Fewer Blacks received well-matched, appropriate size UCB
- Blacks have inferior survival to Whites after UCB transplant (which is not unique to cord blood transplantation)
- Hispanics have similar survival to Whites
- Blacks infused with units with a cell dose > 2.5 and HLA 5/6 match or better have similar survival to Whites
- All patients do better when infused with a higher cell dose

Discussion

Dr. Champlin asked why patient characteristics disease status seemed to be pretty well matched among the three groups. Dr. Rizzo responded that the time to transplant was another variable and the time between diagnosis and transplant was slightly longer in African Americans, but they were relatively balanced for those characteristics. Dr. Champlin noted that was an interesting and unexpected finding. He said socioeconomic factors are very important for all kinds of transplants but that was something that could not be considered in this study. Dr. Rizzo pointed out that a much larger study published in 2009 by Scott Baker looking at peripheral blood and bone marrow did adjust for socioeconomic status based on the zip code of recipients. In that study, the hazard ratios were similar and, after adjusting for socioeconomic status, blacks still did worse than whites. The results are consistent. Drs. Champlin and Rizzo said that because of interracial marriage and related issues, trying to collect data on race and ethnicity has become an ongoing challenge. Ideally, the patients themselves would provide this information but that presents a wholly different degree of challenge – even patients themselves have trouble making that attribution.

Dr. Milford asked whether Dr. Rizzo had an understanding of how clinicians made decisions about HLA matching and cell dose and what the implications are for those making policy decisions. He said the degree to which you insist on having a particular cell dose may be limiting the availability of HLA matched units, and degree to which you insist on HLA matching might mean you have to accept a unit in the real world that is a bit lower in cell dose. Dr. Rizzo responded that there may be situations where a greater cell dose is important depending on the disease. He noted that this is an evolving field where we continue to learn more. An interesting study would be trying to understand the decision making made by clinicians throughout transplant centers and what drives those decisions. Dr. Rizzo said he would expect there to be substantial variability among centers. Making these decisions is very difficult. From an outcomes registry, we don't have all of the information to address those questions.

Joanne Kurtzberg, MD, said there is a huge degree of variability among centers in how people make these choices. You have to make the best choice you can today and drive toward higher cell dose units for African Americans in the registry.

Donna Regan, MT (ASCP), SBB, asked whether the study was able to tease out some of the comorbidities that may have impacted long-term, overall survival. Dr. Rizzo said they did not collect this information and did not look at the data that was available with any rigor.

Dr. Jeffrey R. Schriber, MD, noted that the patients in the study were primarily a pediatric group and wanted to know whether the data would hold true for older patients. Dr. Rizzo responded that the numbers were too small to look at a particular age range.

Mary Horowitz, MD, MS, FACP, said that what needs to be kept in mind in looking at these data is that we're looking at intermediate resolution AV and high resolution DRV1. The more patients we analyze with cord blood transplants, no surprise, HLA at other low side and HLA at higher resolution mismatching has an impact. She said that probably the transplants being done in African Americans are much more mismatched if we did more extended typing and higher resolution typing.

Dr. Milford said we absolutely do know that if you type a group of African Americans at low resolution and then look at high resolution typing, the likelihood that there will be a lot of heterogeneity is perhaps in order of magnitude more than if you do the same thing in Caucasians. This is just the way things are, so the bottom line message will probably be a foregone conclusion.

Susan Stayn, JD, wanted to know whether there is a central repository of information about which centers are doing what at any given time, given the fair amount of variability among centers. She noted that it takes families and patients a lot of time to research this kind of information on their own.

Elizabeth Murphy, EdD, RN, said the NMDP provides information including a transplant center directory with information on all of the transplant centers in the program's network. They use data provided from the CIBMTR to show the differences in what transplant centers are providing in terms of age groups, types of diseases treated, one-year survival and other information. Information is also provided about whether or not the centers are doing cord blood transplants.

Ms. Grant said a requirement was recently added in transplant center participation agreements with network members for transplant centers to refer patients to the Office of Patient Advocacy to learn about protocols if they do not do something in particular at their center.

Ms. Murphy said that through the NMDP Office of Patient Advocacy and patient services area, there are staff that talk with patients, their families and health care professionals on a daily basis. In addition to the print materials and information on the website about what transplant centers provide and the variation across centers, staff talk with individuals directly and try to get them the information they need.

Dr. Kurtzberg said most people find the information they need from networking on their own and from the Internet. Dr. Rizzo said the HRSA website also has information available and connects to other resources available through the program. In response to a question by Dr. Champlin, he said he did not know how many hits the website gets.

Advancing Hematopoietic Stem Cell Transplantation for Hemoglobinopathies: Work Group Report

Bertram Lubin, MD, Work Group Chair

Dr. Lubin said no vote is required because the Work Group is new. Dr. Milford noted that Dr. Lubin will rotate off the Council and said he hoped he would continue to be heavily involved in its work.

The charge to the Work Group is to identify barriers to transplantation and opportunities to more fully realize its potential for individuals with sickle cell disease and thalassemia. The Work Group first convened in March 2012 and held a second conference call in April 2012.

Dr. Lubin said we can say that transplantation has led to a cure for sickle cell disease. Sibling allogeneic bone marrow and cord blood transplantations have successfully engrafted and cured sickle cell disease and thalassemia in patients who received myeloablative conditioning regimens. To decrease transplant-associated toxicities, a variety of reduced-intensity conditioning regimens have been explored and are currently being studied. Risks have to be weighed against the benefits. We need to look at overcoming complications such as graft rejection and graft-versus-host disease (GVHD).

The National Institutes of Health (NIH) is conducting several clinical trials for sickle cell disease, among them:

- Evaluating the Safety and Effectiveness of Bone Marrow Transplants in Children with Sickle Cell Disease
- Nonmyeloablative Haploidentical Peripheral Blood Mobilized Hematopoietic Precursor Cell Transplantation for Severe Congenital Anemias Including Sickle Cell Disease and Beta-Thalassemia
- Stem Cell Transplantation in Older Patients with Sickle Cell Disease

Some of these studies have been stopped, some have had other problems, some are continuing and new ones are being developed. There are a lot of data and publications in this area and Dr. Lubin recommended devoting a significant amount of time at the next meeting to this subject to review the data and figure out where we are. The national initiatives supporting research in this area are very exciting and an alignment of this committee with the committees at the National Heart, Lung and Blood Institute (NHLBI), the American Society of Hematology, the Centers for Disease Control and Prevention (CDC), HRSA and other organizations is a great opportunity to put together a combined group to look at challenges, limitations and where investments should be made. This certainly addresses areas of minority health and health disparities and is a good way to demonstrate how to address these issues.

The Work Group, during its last conference call, identified several issues worthy of discussion:

- Identify long-term predictors of clinical outcomes (be able to predict these complications genetically at birth)
- Streamline the process and infrastructure to promote wider participation in clinical trials
- Examine family attitudes and consenting procedures
- Consider ethical/risk benefit as part of the clinical trial design
- Identify barriers to payers authorization, especially if part of a multicenter trial
- Converge transplant and hematology provider attitudes in regard to the value of transplantation
- Investigate immunobiologic factors affecting transplant, including engraftment and GVHD

Dr. Lubin outlined the following scientific questions for consideration:

- Donor selection
- Unrelated transplants
- Goal of chimerism
- Assessment of immunologic status regarding transfusions, splenic function and iron burden
- Timing of transplant: newborn, following complications, adults with major complications, transfusion history
- Hematologist willingness to discuss transplant option
- Family understanding
- Risk of rejection, GVHD, morbidity and mortality
- Donor pool increase by social solicitations based on potential for cure

The Work Group's ultimate goal is to formulate a recommendation to the HHS Secretary with suggestions that will advance the field and increase the possibility for cure for patients who have sickle cell anemia or thalassemia.

Discussion

Dr. Lubin said that if we develop therapies and protocols that lend themselves to applications in third world areas, we will be the leader in doing a global health initiative that the Gates Foundation or other places would find to be of great value. We're not there yet but it can be done.

In response to a comment about raising the visibility of this issue among those outside the transplant community, Dr. Lubin said pediatric organizations and other groups would follow the lead of NHLBI. He also suggested taking advantage of faith-based organizations to discuss this issue with their congregations. He said most families he speaks with do not deliver at sites where there is a cord blood program.

Richard P. McQuellon, PhD, asked Dr. Lubin what he would recommend to move this field forward. Dr. Lubin said community and family awareness of what is going on is

important, as well as funding for clinical trials. He noted that we are at a unique time. With the strategic plan from the NHLBI as well as a new Institute director coming in, the next several years should be a major change in the outcome and opportunity for transplants.

Scientific Factors Necessary to Define a Cord Blood Unit as High Quality: Work Group Report

Joanne Kurtzberg, MD, Work Group Chair

The Work Group had no recommendations.

HRSA asked the Work Group to recommend criteria for NCBI funding and to address other issues. The group has addressed many issues but continues to wait for results of an analysis from CIBMTR to complete its work. The Work Group continues to accrue data to answer questions regarding cell count requirements:

- Is TNC the best parameter to use for cord blood selection or the best predictor of cord blood potency?
- Do processing, storage and thawing methods impact unit potency?

Some of this group's work overlapped with that of the Working Group to Realize the Potential of Cord Blood. The Work Group had three conference calls between November 2011 and April 2012.

Dr. Kurtzberg said many people worked to try to get the Food and Drug Administration (FDA) to broaden its language so as not to limit people's ability to get a cord blood transplant. The language for indications for use of unrelated donor cord blood units distributed for allogeneic transplantation under license or investigational new drug application (IND) was modified to allow access to cord blood donors for patients with all diseases currently treated with hematopoietic stem cell transplantation (HSCT). The modified language reads "The CCBB will support the access and distribution of licensed cryopreserved HPC (CB) units for disorders affecting the hematopoietic system that are inherited, acquired, or result from myeloablative treatment."

The Work Group previously recommended implementation of a transition plan, on or before October 20, 2011, to allow time for the NMDP and transplant centers to implement changes needed to go through local IRBs. During this transition period, the FDA can continue to exercise regulatory discretion for patients with active, ongoing searches or active donor workups until these transplants are completed, causing less disruption of medical care. These actions were initiated and are in various degrees of execution in U.S. transplant centers.

The Work Group also recommended that CBUs collected through distribution of kits sent to motivated maternal donors, collected by their OB provider, which meet all NCBI/FDA qualifications, be eligible for licensure and listing on the NCBI with the goal of enabling more donations and with decreased collection costs. This recommendation remains under consideration by NCBI and HRSA.

Additional issues that remain problematic and could be addressed by the Working Group include the questions of:

- Multiple INDs
- Recipient consent – the harmonization of consent requirements
- Minimizing the burden of consent in the licensure environment, particularly for collection of cord blood

Future topics for the Work Group to address include:

- Release criteria (under study through the NMDP)
- Outcomes analyses to determine whether there's a need to reassess 'high quality' technical parameters (awaiting CIBMTR analysis)
- Expiration dates and ongoing stability
- Simplification of consent for collection of cord blood

Cord Blood Thawing and Washing: Work Group Report
Jeffrey McCullough, MD
The Work Group has no request for a specific action or vote.

The Work Group on Transplant Center Laboratory Activity was established for a number of reasons, a major one of which is to focus on cord blood banks, banking processes and related issues (not just thaw, wash). Dr. McCullough said the group's charge is to address consistent, safe practices for cord blood handling by transplant centers. Thawing, washing and transfusing the product vary considerably among the transplant centers. Other issues are:

- Some/many transplant center staff are not formally trained in procedures
- Transplant centers use processing recommendations from the bank inconsistently
- Reporting of infusion-related adverse events is incomplete and inconsistent
- Many transplant centers are not adequately prepared for cord blood processing and infusion of cord blood that they would receive from the bank

Some of the points for consideration at the time, prior to the formation of this Work Group, were to:

- Formalize guidelines for single and double infusion
- Reduce number of different thawing protocols
- Require transplant centers to validate procedures they were using for processing cord blood
- Ask accrediting agencies to create relevant standards
- Improve centralized reporting of infusion-related adverse events
- Create a training program for cord blood thawing
- Require transplant centers to train on thawing techniques

Based on those points, additional ones followed:

- Consider a randomized trial comparing thawing versus washing
- Recommend that transplant centers identify backup CBU

- Work with NMDP, CIBMTR, and Bone Marrow Transplant Clinical Trials Network (BMTCTN) to strengthen thawing, processes and training
- Ask AABB and FACT to enhance inspection activities related to thawing and transfusion
- Publish a white paper on cord blood thawing and infusion
- Create a cord blood thawing work group

Dr. McCullough said the Work Group is addressing the following issues:

- Recommendations for Transplant Center Laboratory activities
- Efforts to summarize wash-related data and experience
- The role of cryopreservation and transplant center processes on clinical outcomes
- The system to identify and strengthen reporting of infusion-related adverse events
- The importance of bank and transplant center lab interactions

The Work Group developed issues for transplant labs that the Council discussed and accepted two meetings ago. Other Work Group activities include a review article that is underway; a CIBMTR study, which is in development; and conversations to urge the NMDP to seek ways to bring more focus to transplant lab activities and for NMDP to establish adverse event reporting.

The Council accepted the following Transplant Center Laboratory-related Activities, which were shared with the NMDP:

- Advance communication between cord blood banks
- Receipt and inspection of unit
- Storage of the unit
- Preparation of transplant center lab before transplant
- Quality control of the process and critical values
- Infusion of the CBU and nursing care of the patient

The Work Group's resolution from the previous Council meeting was that the Council recommend to HRSA that the 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**.**

The more detailed status of some of these issues is that there are several methods of handling and thawing the CBU:

- Bedside thaw and infuse
- Laboratory thaw, dilute and infuse
- Laboratory wash
- Other versions of this

Salem Akel, PhD, from the St. Louis Cord Blood Bank/Progenitor Cell Laboratory has agreed to do a literature review and white paper on this topic, which is underway. A draft should be ready by June 1.

The clinical impact of processing methods refers to processing at the bank. The CIBMTR has been trying to identify how they might analyze the clinical outcome in patients in relation to these processing methods:

- Bank processing, cryopreservation and storage
- Transplant center storage, thawing and processing
- Clinical impact of bank processing methods

Dr. Ballen is the principal investigator for a clinical outcomes study that will be carried out by CIBMTR. The study will use existing CIBMTR patient follow-up systems and data. A protocol is being developed.

The Work Group wants to discuss and decide whether to bring before the Council for consideration whether to apply more pressure through the accreditation process for increased standardization or rigidity and to introduce training and quality systems into laboratories. The Work Group feels it has not accomplished all of its objectives and believes the group should continue.

It would be helpful for the Council to provide guidance on whether the Work Group should put more emphasis on transplant laboratories or whether this is not such a big issue. Dr. McCullough said his bias is that this issue warrants further attention.

Discussion

Ms. Regan said there is published data on a couple of different methods, primarily the wash method, the reconstitution method and some people doing it at straight at the bedside. There is no one procedure that is going to fit all cord bloods because they are manufactured differently, so a transplant center has to really pay attention to the kind of product it gets. We can standardize the different methods that are currently available. There can be one template for a wash procedure and one template for a dilution procedure. We are probably going to recommend three different methods and the transplant center is going to have to validate those methods.

Dr. Milford asked what role the Council should play as an advisory group in this matter. Dr. McCullough said the Work Group would bring specific recommendations to the next meeting, and the Council can urge accreditation systems and NMDP to address some specifics in their processes that we will bring back to the Council. Dr. Champlin suggested workshops during national meetings to train laboratories in optimal methods. Robert Hartzman, MD, suggested a study to determine what methods are optimal before making any recommendations. Ms. Regan said the paper will include information as to why one method is preferable to another.

Dr. Horowitz said processing approaches and graft characteristics over a 10-year period will be examined. The biggest stumbling block was getting agreement on what to look at, and the extent of data available is now being evaluated. She said she hoped to have the final data set ready by the end of this calendar year. The group should be able to see some results when they convene next May.

Dr. Milford said the Work Group should go forward but that they need to be careful about making specific recommendations without data.

Adverse Event Reporting
Willis Navarro, MD, NMDP
No action items are requested of the Council.

Dr. Navarro said the event reporting system (ERS) that NMDP created, FormsNet2, has been broadened to add all NMDP-facilitated cellular products as of April 15, 2012. It now includes cord blood, T cells, marrow and PBSC. The benefit of this change is that it consolidates a single point of reporting for transplant centers to be able to report adverse events and product complaints for any product. Transplant centers are already familiar with this system.

Once an event is entered, the NMDP provides event notification to the stakeholders (CBBs, IND holders, network as applicable) when there is a pertinent adverse event. The system enhances the ability to comply with all reporting obligations. Having a single source of event submission allows tracking and trending of events, producing more timely network notification. It also allows for more root cause investigation and remedial/corrective interventions.

Transplant centers are reminded about training opportunities for adverse event and product complaint reporting through network announcements. There are links to training materials sent via NMDP network announcement to two sites regarding what reporting needs to be done and how to do the reporting. As of April 12, 2012, 100 participants have completed adverse event training, representing a total of 75 transplant centers.

Of five adverse events reported through the ERS between Oct. 17, 2011, and April 6, 2012, two were actually adverse events and three were misreports. During that same time period, 51 product complaints were reported through the system. Fourteen product deviations from cord blood banks also were received.

Dr. Navarro said the NMDP is pretty comfortable that they are receiving reports and things are working well. The system has been well-received by the transplant centers from what they have heard, and reported events are on pace with expectations.

Discussion
In response to a question about labeling errors, Dr. Navarro said the vast majority of labeling errors were trivial from the patient safety perspective. In response to another question, Dr. Navarro said he did not know how many units were imported, although they were the minority.

In response to a question about data reporting, Dr. Navarro said they are looking at the pattern of data to figure out how best to report it, since this is a relatively new system. An annual report is the most appropriate way to present the data unless there is an event that requires earlier notification. Network notification and presentations at meetings where pertinent stakeholders are present would be the way to get the word out about adverse events that needed to be reported in a timely manner.

Dr. Milford suggested giving thought to what the process would be for ongoing analysis, not just reporting on an annual basis. What kinds of ongoing analysis would you be doing and what

triggers would you have to do the sort of additional levels of investigation for systematic problems that need to be corrected in a timely way – or if there is a serious problem that needs to be addressed. He suggested that Dr. Navarro bring ideas about this issue back to the Council.

Dr. Navarro said there is no plan to audit transplant centers. In response to a question about who files the reports, Dr. Navarro said it could be anyone from a transplant physician to laboratory staff or nursing staff, if they have observed something. It is up to the transplant center to determine how reporting should occur.

Update – Advisory Committee on Blood Safety and Availability

James Berger, MS, MT (ASCP), SBB, Executive Secretary, ACBSA

Mr. Berger described the responsibility of the ACBSA, which is to advise the Secretary of HHS through the Office of the Assistant Secretary of Health on a range of policy issues.

There was a discussion of informed consent for recipients of blood, organs and tissues at the December ACBSA meeting. The preamble that the committee had going into the meeting was that:

- All patients are entitled to be informed that they are receiving a substance of human origin, such as blood, organs, cells and tissues
- A robust process of informed consent for recipients of transfusion and transplantation is an ethical imperative

The committee found that:

- Practices of informed consent for transfusion and transplantation are highly variable
- Practices of informed consent in many instances appear to be inadequate to properly engage patients in shared decision making
- Gaps exist in
  - data on the risks of transfusion and transplantation and their alternatives
  - Current knowledge and communication of risks, benefits and options by persons obtaining informed consent for transfusion
  - Current knowledge and communication of donor-derived disease transmission risks by persons obtaining informed consent for organ transplantation
  - Knowledge of informed consent practices for the wide spectrum of tissues for transplantation
- Training (e.g., physician and other health professional) in the need for and processes to achieve appropriate patient informed consent is inconsistent and generally inadequate
- The Centers for Medicare and Medicaid Services (CMS) require patient informed consent for organ transplantation and do not require specific patient informed consent for transfusion and tissue transplantation
- Disclosures of risk are generally inadequate
- Unnecessary transfusions contribute to the risk of the transfusion process

The committee recommended that the HHS Secretary:

- Direct CMS to establish requirements for patient informed consent for transfusion and tissue transplantation

- Establish a working group to cooperate with stakeholders to identify opportunities and strategies to improve informed consent for transfusion and transplantation recipients
- Support research on optimizing patient informed consent for transfusion and transplantation
- Provide funds to address identified gaps
- Enhance funding for the National Healthcare Safety Network (NHSN), Scientific Registry of Transplant Recipients (SRTR) and the Organ Procurement and Transplant Network (OPTN) to support biovigilance efforts (donor and recipient)
- Promote best practices in patient blood management including Computer Physician Order Entry (CPOE) to reduce unnecessary transfusions

The committee's next meeting will be held on Dec. 6 and 7, 2012.

Discussion

Dr. Horowitz asked whether the committee differentiated between tissue products and transfusions and whether they considered this issue in the context of differences between these activities that take place within the trial or outside the trial. Mr. Berger responded that the committee brought in subject matter experts because the committee's composition does not include specific tissue representation. He said they did not break activities down by trials because of a lack of time but that is something that could be looked at.

Dr. Horowitz said the notion of informed consent is absolutely crucial and that it is important for the committee to discuss whether they are recommending standardized language. Patients may be confronted with 14 or 15 documents at once. They need to have flexibility in what you would expect in an informed consent process because the patient is not just having a transfusion but maybe multiple things that require consent. Mr. Berger responded that the working group has taken into account that there are a lot of things that cannot be standardized.

Dr. Milford asked whether there was any precedent for a nationwide common consent procedure for something that might be a local procedure. Mr. Berger said the working group was charged with looking at this but because of the variances involved felt it was not something that could be standardized across the field.

Circuit Court Decision

Mark McGinnis, Counsel to the ACBSCT

Mr. McGinnis discussed Flynn versus Holder. The Ninth Circuit holds that bone marrow donors may be compensated, depending on the method of donation used (apheresis). Mr. McGinnis said the decision was a surprise to virtually every lawyer working on the case. Most nations we trade with have outlawed the buying and selling of this tissue source. Mr. McGinnis said the Court's opinion does not force anyone to work with a paid donor, or the government or anyone else to start paying donors. The opinion does not just cabin itself to scholarships to donate marrow but allows for any kind of payment to be sought at really any point up to donation (problem of once in the system).

HHS and the Department of Justice (DOJ) sought rehearing en banc (all Ninth Circuit judges), which was denied. The DOJ has until early July to decide if it wants to seek Supreme Court Review. HHS is actively exploring the possibility of writing a rule to correct the court's error.

Discussion
Mr. McGinnis said people might start asking about compensation and that this decision could impact the number of altruistic donors. Council members agree that donor compensation is a bad idea. Dr. Milford asked if there were suggestions on how the Council might proceed on this issue. A member of the audience suggested that the Council consider making a recommendation that the Secretary support any reasonable effort to ensure that compensation for donation of marrow, peripheral blood stem cells, cord blood or other similar products continue to be banned.

Dr. Milford called for discussion on the proposed recommendation. Dr. Champlin said the letter should indicate why compensation should be banned: the effect it would have on altruistic donations, concern about the quality of cells collected and infectious complications, and concern about donors with high-risk behavior who are desperate for money (which could lead to transmission of infection). Also if this policy is begun with unrelated donors, it could spill into sibling donations (where a donor might want to charge a sibling $10,000 for a donation).

Dr. Milford asked that a recommendation letter be prepared to the Secretary for review by the Council later that day outlining the Council's concerns about the recent decision of the Ninth Circuit Court of Appeals in the matter of Flynn, et al v. Holder stating that the National Organ Transplant Act does not prohibit compensation of peripheral blood stem cell donors which raises a number of concerns regarding the access to and safety of blood stem cell donations.

Access to Transplantation: Work Group Update on Technical Expert Panel: Insurance Guidelines/Covered Diagnoses and Costs
Richard Champlin, MD
Dr. Champlin said the ACBSCT committee has agreed that a consensus document be developed as guidance to the industry listing the current accepted indications for HSCT. The goal is to develop concise "general guidance" to the public, physicians and insurance industry. HSCT is a rapidly developing field where innovations are improving patient outcomes. The ACBSCT has passed a resolution supporting insurance coverage of standard care cost while participating in clinical trials. Dr. Champlin said there is general agreement in the principles of HSCT and its potential to cure a broad range of diseases. However, there is a diversity of opinion on precise indications for each diagnosis, given disease prognosis, and the risks and efficacy of HSCT.

Discussion
Dr. Milford asked what the Work Group's product is and to whom would it be directed.
Dr. Champlin said the product is an expert panel summary of guidance that would be submitted to a peer reviewed journal, such as *Blood*, for publication, as well as for posting on the HRSA website. Patricia Stroup, MBA, MPA, asked whether Dr. Champlin had contacted the European Union (EU). Dr. Champlin responded that the EU published a paper in 2009 and that the Work Group referenced their material and used their report as a starting point to expand their own analysis. He said their recommendations did not differ much from that of the Work Group. Dr.

Champlin said volunteers interested in this issue should be invited to the next Work Group meeting. Dr. Milford said Council members should contact Patricia or him regarding their thoughts on who should be on this committee.

Unmet Need

Jeffrey Chell, MD, NMDP

There were no recommendations or required actions.

Dr. Chell provided an update on work regarding access to transplant and further delineating what the need for allogeneic transplant is in the U.S. and the system capacity initiative is trying to identify and articulate for individual transplant communities what the need is in their community and how to work together to meet that need. The need is considerably greater than what hospitals feel they have the capacity to provide.

The NMDP system capacity initiative is a three-year effort trying to identify barriers to transplants outside the NMDP. By applying the optimal transplant rate to the U.S. population, the need for allogeneic (related and unrelated) transplant is 18,000 per year (5,500 per year related and 12,500 per year unrelated). With expanded indications and age ranges, the calculated need for unrelated transplant has increased 25 percent. NMDP-facilitated transplants have doubled in the past five years and grown 2.5-fold for minorities. The data show that access for unrelated transplant has improved, but the same cannot be said for related transplants.

Regarding the question of whether access to transplants in real terms has improved, Dr. Chell said "yes." He shared the following findings:

- There is a positive, statistically significant, correlation between allogeneic transplant and average household income and average household healthcare expenditures.
- There is a negative, statistically significant correlation between allogeneic transplant and ethnicity, but the correlation coefficient is half that of income and expenditures.
- There is more analysis to be done (separating out malignant from nonmalignant disease), but for allogeneic transplant, it appears that money trumps ethnicity.
- More focus is needed on optimal referral, insurance coverage and other barriers that limit or delay initial access and progress.

The conclusions drawn from the analysis are that the:

- Analysis may aid in capacity planning for regional healthcare
- Model will work for other diseases or procedures
- Analysis needs to be validated with multiple transplant center visits
- Initiative may help transplant program directors access capital for growth

Discussion

Dr. Lubin remarked that there is uncertainty about what reimbursements are going to be because of health care reform. He also said we need to be thinking about how to keep costs down while providing services. Dr. Chell responded that we do not know what the impact of health care reform will be any time soon. However, the expectation is that reform would increase access but lower average reimbursement so that you would get a little less than you are getting now per case but there would be a broader group of people. This means the economic impact might be positive

if you currently provide a lot of free or no-pay care. He added that there are not many silver linings to this cloud from a hospital CEO standpoint.

Advancement in Cellular Therapies

Dr. Rizzo thanked Dr. Milford and Ms. Stroup and the HRSA staff for allowing the CIBMTR to bring this topic regarding cellular therapies before the Council. The group is seeking advice and recommendations from the Council regarding the following:

- In the short term, what scopes of indications for cellular therapy or types of cells infused should be the focus of the C.W. Bill Young Cell Transplantation Program? How broad or narrow should we be thinking about this?
- What recommendations does the Council have in the short term for the CIBMTR regarding strategies and suggested contacts that would enhance our ability to collect the data from nontransplant indications for cellular therapies if these are considered appropriate in scope?
- Would the Advisory Council wish to appoint a subcommittee to make additional recommendations both to HRSA and to the contractors for the program to help with the following challenges:
    - What should be the scope of indications for cellular therapy to be corrected by the program?
    - What recommendations does the Advisory Council have for the program to best achieve that proposed scope and how can the program assure participation from entities performing procedures considered to be within the scope for the program, especially when indications are not directly related to hematopoietic reconstitution?

Dr. Rizzo said the next three speakers would lay out the background for this topic: Dr. John Barrett will speak about cellular indications that are related to hematopoietic reconstitution; Dr. Armand Keating will discuss the universe of all the other applications of cellular therapies; and Dr. Marcelo Pasquini will discuss how the CIBMTR has tried to address these challenges.

Overview of Current Indications and Future Potential of Cellular Therapies in Hematology, Malignancy and Post Hematopoietic Cell Transplantation

John Barrett, MD, Chief, Stem Cell Allogeneic Transplant Section, NHLBI, NIH

Dr. Barrett said the challenges related to stem cell therapy include relapse, infection, organ toxicity and GVHD. He said the way in which cell therapy is being used can be organized into four levels:

- Level one is where we are today and relates to the minimal manipulation of bone marrow, umbilical cord blood, G-marrow, G-blood and how cells have been processed.
- Level two is related to cell selection technology. Today's technology is continually developing and expanding indications, is easily deliverable and commercially robust.
- Level three relates to cell culture expansion, which is much easier to do today than it was 10 years ago. Emerging technologies are making it simpler and more applicable.
- Level four is related to gene insertion, which involves some sort of gene manipulation to improve the quality of the cells. There is promising emerging technology, broad application and significant regulatory hurdles for gene insertion.

Dr. Barrett outlined the roadblocks for cell therapy, which include:

- Acceptance: cells are not widely believed to be an effective reliable therapy (an important exception to this is antigen-specific T cells, which are very effective)
- It is largely unproven in phase 3 trials (although there are some phase 3 trials)
- It involves complicated, expensive systems that need regulatory supervision (but technologies are getting easier to understand and regulation is becoming more routine)
- Individual "boutique" application dissuades corporate involvement (third-party cells are used in some indications)
- Limitations of manufacturing strategies (there are some models of manufacturing, such as the GMP center and factory models)

Dr. Barrett said successful clinical cell therapy trials require no immediate adverse effects; no distant side effects; at least 50 percent efficacy; demonstrable cost savings over conventional treatments; and reproducibility in different centers. According to Dr. Barrett, cell processing can be made much easier and much more general in about 10 years' time.

Overview of Current Indications and Future Potential of Cellular Therapies in Regenerative Medicine

Armand Keating, MD, FRCPC, Director, Cell Therapy Program, Princess Margaret Hospital

Dr. Keating said there is burgeoning activity in cell therapy. There has been a convergence of diverse fields over the past 20 years to move this field forward. Many clinical trials are underway worldwide, which makes cell therapy exciting. The vast majority of trials are either phase 1 or phase 2; very few phase 3 trials are being undertaken.

More than about 4,000 persons have received mesenchymal stromal cells (MSCs) for many disorders, but fewer than 600 patients have been reported in the peer review literature. Measuring clinical activity is a challenge. According to clinicaltrials.gov, there are 1,223 clinical cell therapy trials involving hematopoietic cells; 280 involving neural cells; 156 involving mesenchymal stromal cells; and three involving embryonic cells.

Dr. Keating concluded that activity in cellular therapy has the potential to be enormous, but we need a homerun. He said that bone marrow transplantation was a homerun but he thinks we are close to that with some aspects of cellular therapy. Clinical activity and research align either with very specific programs or subspecialty programs that are difficult to access by members of the traditional BMT community. That access will be further attenuated by the use of non-hematopoietic cells, like cardiac or neural stem cells, where individuals such as ourselves will be totally unnecessary.

Overview of CIBMTR Data Collection for Cellular Therapy Indications, Remaining Challenges

Marcelo Pasquini, MD, MS, Medical College of Wisconsin

Dr. Pasquini said the objective of the CIBMTR cellular therapy initiative started under the CIBMTR contract with HRSA to understand the long-term outcomes of cellular therapies. The initiative would:

- Study uses of tissue specific progenitor and stem cells for indications *other than* hematopoietic recovery, reversal of inborn errors of metabolism or treatment of primary immunodeficiencies
- Provide an infrastructure to allow long-term follow up of patients treated on cellular therapy trials

Over the past five years, the initiative conducted center surveys, reached out to the cardiovascular community, collaborated with Production Assistance for Cellular Therapies (PACT) on data collection, launched the cellular therapy registry, organized an interest group in cellular therapy and formed the Cellular Therapy Working Committee.

The system for data collection included voluntary reporting; a short registration-type form; a unique ID assigned to all recipients; and electronic data collection. The trigger to collect the form may be applied differently depending on the center (for instance, a transplant center involved in cellular therapy for regenerative medicine versus a cardiovascular center).

The initial summaries and capture of data has shown that the survey mechanism was inefficient to capture activity; collaboration with other disease specialties is challenging because these studies are early so it is hard to share data; and data reporting to the new cellular therapy registry is limited to a few transplant centers.

In order to expand data collection and the registry, collaboration with manufacturers is necessary, as well as the development of forms to capture new cellular therapy indications, outcomes data collection for selected indications and capturing activity for government-sponsored projects.

Discussion
Dr. Milford wanted to know what our charge is from the 2010 statute. The wording says cellular stem cell therapies are what we are supposed to be collecting information about. While that does not mean we cannot go beyond that, we should be focusing on that issue first. Dr. Pasquini responded that the language has changed over the years. It is not clearly defined and the scope of the initiative is not clear. Since we are not sure what information we should be collecting, we cast a wide net. We wanted to look at indications that are mostly done so we could capture that activity, but we also wanted to look at what the transplant field is moving toward, which is T-cell-related indications. One charge for the Council is to guide us to understand the scope of what information we need to collect.

Dr. Champlin said cellular immunotherapy that Dr. Barrett talked about is the natural extension of allogeneic transplants because it works through immunologic mechanism – the graft versus tumor effect. Reconstitution is a major part of allogeneic transplants, and fighting infections and cell manipulation to try to enhance those antitumor effects in immune recovery for infections is the natural evolution of the field – so that is clearly within the purview of CIBMTR and the committee. Stem cell is in our title and also seems to be within the purview of the committee.

Claudio Anasetti, MD, said he would advise CIBMTR to do what it is best at and focus on transplant centers, stem cell transplantation related to malignancies, etc., instead of cell therapy centers. Tissue repair might not be the core expertise of this group. He said there will be gray

areas, such as what to do with T cells, and that these middle-ground areas that we are familiar with can be addressed separately.

Dr. Horowitz said CIBMTR would like the Council to provide more specific direction. She said the group has been trying to reach out to communities that are not natural constituencies in trying to address this area of activity. However, we need to come to some consensus on where we can best offer value because we want to show we have data, we are engaged in the community and we are answering questions the community wants answered.

Dr. Kurtzberg said we have a lot to offer other specialties coming into cell therapy because they do not have familiarity with the regulations, quality assurance, cell manufacturing, etc. Helping these communities learn how to deal with cells and how to handle them properly is one thing. Another thing is that these other groups do not have an outcomes database.

Dr. Horowitz said the CIBMTR contract may stipulate that they have to collect the data, but there is nothing that says other groups have to provide it. The field is at a very early stage and the studies are small and often being done with corporate support, so there are intellectual property issues. In addition, sharing data is not at the top of anybody's priority list right now.

Ms. Harvath said language could be included requiring recipients of government funding for cell therapy studies to share or report their data to CIBMTR and similar groups so there is no duplication of government paying for two separate databases to be created. This requirement would be included up front and a part of the funding award. This approach would engage the funding organization.

Dr. Horowitz agreed with Ms. Harvath that a problem with sharing data with CIBMTR and other groups is that the data generators are afraid they will lose control of their data and how it is reported. The other issue is that data collection is a lot of work and there is no money for it. Even if people see the value, it adds a huge burden that is not funded by anyone.

Dr. Champlin said in cell therapy every product is different – how it is manufactured, how it is genetically modified, what the target is – so it is not clear what data to collect because it is going to be evolving so rapidly over time that you would hate to put a great deal of effort into data that is meaningless because it does not have sufficient detail in the end.

Dr. Milford said the real question we have to wrestle with here is what we should be telling HRSA what are the priorities – what do we feel falls within the sphere of what we should be collecting data on and what things we do not have to deal with right now. That is the kind of information that both HRSA and CIBMTR need.

Dr. Kurtzberg said they should track nonhomolgous use of hematopoietic cells.

Ms. Grant said the law says the database is required to collect information on marrow, cord blood and other products from a donor. Regulations are possible to clarify things so you have something to present to the transplant centers. However, a regulatory process can take a long time and we do not want to interrupt the data collection process. Ms. Grant said the Council

needs to be aware of the risks of going down that [regulatory] road and that she is open to any suggestions the Advisory Council has.

Dr. Champlin said the Council is fully capable of collecting hematologic transplant activity that was discussed today, but it is not set up to collect the more exploratory applications of stem cell therapies and immunotherapies. Dr. Milford said it sounds like this issue is something that needs to be continually thought about and that discussions with HRSA and CIBMTR need to occur. He said he would like a working group on what the scope should be and everyone can contribute to it. We also need to find a person willing to chair the group. He said we will appoint a chair and interested volunteers should let Patricia know.

The Council reviewed the recommendation regarding the Ninth Circuit Court of Appeals decision. Dr. Milford made a motion to amend the language to read "by the registry" instead of "be the match." Dr. Champlin said the language included all of the concepts discussed earlier. The Council approved the recommendation. (See copy of the recommendation.)

Public Comment

Dr. Fran Verter from the Parent's Guide to Cord Blood Foundation wanted to know what could be done to make the white paper Dr. Champlin discussed enforceable – how third party payers could be encouraged to follow the consensus for transplantation indications. Dr. Champlin said that while the Council has no enforcement capacity, it hopes insurance carriers will make decisions based on the best available medical information and that most large insurance companies will cover things included in accepted guidelines. Dr. Milford said insurance companies have been involved to some degree in the process already and will be in the future.

Conclusion and Adjournment

Since there was no other business, Dr. Milford adjourned the meeting at approximately 3:40 p.m.

Attachments

1. Summary of Council Decisions
2. List of Attendees

Attachment 1: Summary of Council Decisions

Cord Blood Thawing and Washing
Dr. McCullough asked for the Council's guidance about whether the Work Group should continue to pursue the issue of transplant center laboratory activities. Dr. Milford said the Work Group should proceed in its efforts but should be careful about making specific recommendations without supporting data.

Adverse Event Reporting
Dr. Milford asked Dr. Navarro to think about a process for ongoing analysis for reporting adverse events, rather than just reporting the data on an annual basis. He asked Dr. Navarro to bring ideas back to the Council about how to report systemic problems or serious problems that need to be addressed in a timely way.

Circuit Court Decision
Dr. Milford asked that a letter to the HHS Secretary be prepared for review by the Council later that day outlining the Council's concerns about the Circuit Court decision. Council members reviewed the letter and approved the contents with one amendment (to strike "by the match" and insert "by the registry").

Advancement in Cellular Therapies
In response to a request by the CIBMTR for guidance on the extent to which it should address cellular therapies, Dr. Milford asked for volunteers to form and chair a working group on this issue. He said Council members should let Pat Stroup know if they are interested in volunteering and that he would appoint volunteers if necessary.