Advisory Council on Blood Stem Cell Transplantation (ACBSCT)
U.S. Department of Health and Human Services
Health Resources and Services Administration
5600 Fishers Lane
Rockville, MD 20852

Meeting Location: Crystal Gateway Marriott
1700 Jefferson Davis Highway
Arlington, VA 22202
Arlington Ballroom, Salon Six
September 13-14, 2016

Day One, Tuesday, September 13, 2016
9:30 a.m.-4:30 p.m.

Welcome and Opening Remarks

Jeffrey McCullough, M.D., Chairperson, ACBSCT

Dr. McCullough called the meeting to order and welcomed all council members and other participants to the meeting. He expressed appreciation for all of the members of the public who were calling in.

Program Report: Division of Transplantation

CAPT Melissa Greenwald, M.D., Division Director, Division of Transplantation, Health Resources and Services Administration (HRSA), U.S. Department of Health and Human Services (HHS)

CAPT Greenwald began by explaining that HRSA's work was authorized by the Stem Cell Therapeutic and Research Reauthorization Act, which reauthorized the C.W. Bill Young Cell Transplantation Program. The goals of this program are to increase both the number of unrelated donor transplants and potential marrow donors and engage in patient and donor advocacy services. Its two additional goals are to educate the public and professionals on transplantation and conduct analysis and reporting of transplant outcomes data.

The National Cord Blood Inventory's (NCBI) goals are to fund cord blood banks for the purpose of increasing the amount of cord blood available for transplantation to at least 150,000 new units, encourage donation from a genetically diverse population, and make cord blood units that are not appropriate for transplantation available for research use.

CAPT Greenwald also issued a 2015 reauthorization status update.

She explained that the program reauthorization requires HRSA to report on the state of the science for using adult cells and birthing tissue to develop new patient therapies and for inclusion in the C.W. Bill Young Cell Transplantation Program. HRSA's Division of Transplantation is asking ACBSCT to consider forming a workgroup to help plan an informational update to the council about the current and future therapeutic use of adult cells and birthing tissues for patients and welcome suggestions on how to meet this legislative requirement.

HHS is required by law to issue a determination by December 18, 2016, on whether peripheral blood stem cells and umbilical cord blood are "human organs" and, therefore, subject to section 301 of the National Organ Transplant Act, and is working to meet that deadline.

The HHS Secretary also has been directed to consider the best scientific information available to make the highest number of cord blood units available for transplant when entering or extending the period of funding under NCBI contracts.

Moving on to current and recent HRSA activities, CAPT Greenwald explained that HRSA continues to fund cord blood banks' efforts to increase collections at new and existing birthing sites in racially and ethnically diverse communities. Karen Dodson (on behalf of Merry Duffy, who was unable to attend) of the National Marrow Donor Program (NMDP) delivered a presentation on this topic later during the meeting.

HRSA co-sponsored and participated in the National Institute of Allergy and Infectious Diseases' (NIAID) Late Effects Consensus Workshop in June, during which experts discussed evidence and planned research on blood and marrow transplant recipients to improve these patients' monitoring and management. Minoo Battiwalla, M.D., a clinician with the Hematopoietic Transplantation Section of the Hematology Branch of the National Heart, Lung, and Blood Institute (NHLBI) within the National Institutes of Health, provided an update on this conference later during the meeting.

CAPT Greenwald also provided an update on recommendations from ACBSCT's meeting on March 3, 2016.

In connection with the council's recommendation that HRSA engage experts to study the U.S. cord blood banking system to identify current business practices and recommend ways to strengthen its financial operations, HRSA worked with the HHS Office of the Assistant Secretary for Health to award a contract to conduct the U.S. Cord Blood Industry Sustainability Study. The study, which has been funded and will begin this year, will help to inform the blood stem cell community and HRSA on the best way to increase the number of diverse cord blood units available for transplant and how cord blood banks can achieve financial viability and sustainability. HRSA is considering what activities to pursue in response to recommendation 28 through which the council suggested that HRSA adopt a funding framework that provides incentives for collection of high total nucleated cell (TNC) units for a diverse population and acknowledges their higher associated costs. HRSA expects the above-mentioned study to inform this effort.

CAPT Greenwald also discussed factors that were used to prioritize fiscal year (FY) 2016 NCBI funding priorities, which are divided into three tiers:

- Licensed cord blood banks;
- Cord blood banks that are making progress toward licensure; and
- Cord blood banks that are making minimal progress in achieving licensure.

Many of these factors place a high priority on funding collection of cord blood units from people from various racial and ethnic backgrounds, particularly from African-Americans and Asians.

Examples of the Division of Transplantation's additional priorities include identifying additional projects that will:

- Increase the diversity of cord blood units added to the NCBI;
- Assess data on the number of unrelated blood stem cell transplants the C.W. Bill Young Cell Transplantation Program supports;
- Improve understanding of haplo-identical transplants and other therapies; and
- Continue to identify and use available data and resources to inform policy decisions.

HRSA is developing a set of questions to elicit information and data on the evolution of blood stem cell transplantation to inform policy decisions and for which it will seek ACBSCT's input. Potential topics include scientific factors that contribute to cord blood unit quality, the role of cellular therapy involving adult donors and cord blood in the C.W. Bill Young Cell Transplantation Program and ways to increase access to transplantation from diagnosis to transplantation. In support of this, HRSA plans to add staff support to the committee and has posted a job announcement for a biostatistician. CAPT Greenwald welcomed Robert Walsh who is now serving as HRSA's designated federal officer.

Comment

When asked how long the sustainability study is likely to take, CAPT Greenwald estimated that it could be finished within a year.

Another participant asked how the funding priorities that were discussed differed from those in the past. CAPT Greenwald responded that the priorities and how they're organized are probably not very different from previous ones but reflect efforts to make decisions more consciously, focus more on licensure and how contracts are structured and built, and to increase transparency.

Changes to Hospital Outpatient Payment for Hematopoietic Blood Stem Cell Treatments

Lela Strong, Analyst, Division of Outpatient Care, Centers for Medicare & Medicaid Services (CMS)

Ms. Strong provided an overview of the Hospital Outpatient Prospective Payment System (OPPS), which is identified by Healthcare Common Procedure Coding System (HCPCS) codes. She pointed out that the HCPCS codes are assigned to ambulatory payment classifications (APC) based on clinical and resource homogeneity and that the payment rate for each APC applies to the related health care services that are grouped in the same APC, which is called a Comprehensive APC (C-APC). In short, each C-APC covers all primary procedures *and* all adjunctive and secondary services that are provided in conjunction with each procedure. (This is often referred to as "bundling.")

For calendar year (CY) 2017, CMS is proposing 25 new C-APCs, which are major surgery APCs within a variety of C-APC families. Among these is a proposal for an Allogeneic Hematopoietic Stem Cell Transplantation C-APC.

The current APC payment rate for HSCT under APC 5281 is $3,015. Because in the outpatient setting donor acquisition costs are bundled into the APC payment for the transplant procedures, in addition to the transplant, other services the APC payment covers are:

- National Marrow Donor Program fees;
- Tissue typing of donor and recipient;
- Pre-/post-donor evaluation; and
- Preparation and processing of stem cells.

CMS has received comments from stakeholders indicating that the payment for allogeneic hematopoietic stem cell transplantation (HSCT) is inadequate. Stakeholders also stated three issues that they contend make it impossible to convert costs to charges. The three issues include:

- Outpatient allogeneic HSCT is reported on claims that are being identified as multiple procedure claims, which are unusable under the standard OPPS rate-setting methodology.
    - To address the issues stakeholders identified, CMS is including in its FY 2017 Proposed Rule to establish a new C-APC 5244 (Level 4 Blood Product Exchange and Related Services), assign CPT code 38240 (HPC allogeneic transplantation per donor) to the new C-APC, and propose a payment rate for of $15,267. CMS believes that this will allow all the costs of all outpatient services associated with allogeneic HSCT, including donor acquisition services listed on the claim with CPT code 38240, to be bundled into the C-APC payment rate. CMS plans to analyze the costs using its comprehensive cost accounting methodology to establish future C-APC payment rates.
- The revenue code and cost center where donor acquisition costs are reported is not dedicated to allogeneic HSCT donor acquisition costs.
    - In response, CMS proposes to update the Medicare hospital cost report by adding a new standard cost center and create revenue code 0815 (Allogeneic Stem Cell Acquisition Services) to identify hospital charges for stem cell acquisition for allogeneic HSCT and require hospitals to use the code with outpatient allogeneic HSCT. CMS also would discontinue using revenue code 0819 to identify stem cell acquisition charges for allogeneic bone marrow/stem cell transplants. CMS believes that this will result in an accurate estimate of allogeneic HSCT donor acquisition costs for future rate setting for CY 2017 and future years.
- Stakeholders also expressed concern that services may be reported to the same revenue code and mapped to the same cost center code as allogeneic HSCT donor acquisition charges but are not related to these services.
    - Ms. Strong reported that CMS plans to update the Medicare cost report by creating a new cost center to establish a more accurate estimate of costs for allogeneic transplants. This has been included in the latest proposed OPPS ASC proposed rule, which is awaiting public comment.

Comment

John McInnes, M.D., said he began receiving comments from stakeholders when he started as division director with OPPS at CMS in 2011. At that time, HSCT was a relatively new procedure. Since then, other procedures have been introduced and payment coverage has

expanded. CMS is taking steps to provide more accurate payment in the hospital outpatient setting.

ACBSCT member Elizabeth Shpall, M.D., asked whether the $15,267 payment covers all cord blood services, including umbilical cord. When Dr. McInnes confirmed this, she noted that the cost of such services exceeds that amount. Dr. McInnes indicated that he had received many comments on this proposal, including one to adjust claims. CMS will consider this, but he noted that most comments focused on bone marrow.

ACBSCT member Sergio Giralt, M.D., asked whether the same code would apply if a second graft is needed, since the same service would be provided for the first transplant as for the second. He also asked whether there is a limit to how many transplants will be covered over a set period of time (e.g., 30 days). Dr. McInnes did not have an answer, but said he would check with CMS's Coverage and Analysis group to find out.

ACBSCT member Mark Walters, M.D., pointed out that the costs of identifying a donor who is related to the recipient can vary greatly from the costs associated with identifying an unrelated donor. Council member Colleen Delaney, M.D., suggested that this could lead to donor choice being swayed by cost rather than what is best for the patient. Presenter Mary Horowitz, M.D., of the Center for International Blood and Marrow Transplant Research, said that the cost could supplant the selection of related versus unrelated donor and prevent some patients from getting a transplant altogether. The payments will not cover the costs of a related donor acquisition. Dr. Shpall agreed, adding that the payment disparity could discourage physicians from considering seeking an unrelated cord blood donor. Council member Jeffrey Schriber, M.D., said that because allogeneic transplants aren't covered, in some cases these services are not offered at transplant centers. Dr. McCullough, the council chair, pointed out that this is an issue of access and said more discussion is needed.

Dr. Schriber noted that it has been proposed that stem cell transplants be treated the way solid organs are in terms of assigning payments. There is a specific cost for each organ. "It is viewed as a pass-through." He pointed out that peripheral stem cells may ultimately be treated as a solid organ; however, Mr. Walsh pointed out that this peripheral blood is being considered as a separate case that would not necessarily apply to other types of stem cell transplants.

Dr. McInnes said that CMS follows specific statutes in setting outpatient hospital payments and that changing this would be beyond his office's scope. He said that there is no inherent limitation in the payment system and that, if one exists, this is what the proposed rule is supposed to remedy. CMS may be willing to create multiple codes for payment of different subtypes of allogeneic transplants, but each should only include the donor acquisition cost for a particular service — the charges connected to a particular cost must be specific. Other issues are whether the code is correct and appropriate for CMS use. "We have to get to the point where hospital payment rates will correlate with the service," Dr. McInnes said.

Dr. McInnes also said that a suggestion had been made to cull claims that contain inaccurate or incomplete information. If those claims are removed, payment rates will rise. It was also suggested that CMS add an edit that would require a new revenue code specific to donor acquisition.

Council member Mary Hennessey, J.D., said that bundling services is CMS's effort to manage over-utilization and control costs but added that over-utilization is probably not an issue in stem cell transplantation. The challenge lies in finding the right donor match.

Dr. Delaney said there are a lot of publications that look at advantage of one stem cell source over another and that this should be considered over cost, and that the emphasis should be on evidence-based medicine.

Council member Naynesh Kamani, M.D., asked what mechanisms exist to provide feedback to CMS on payment bundling methodology. Dr. McInnes said that the responsibility for payment areas is distributed among various directors. He handles hospital outpatient payment issues. He added that any of the division directors are willing to consider comments.

Dr. Giralt urged ACBSCT to propose a recommendation to CMS stating that $15,267 is not adequate to cover the costs of donor acquisition services, and that this low rate of payment could skew the choice of products toward less costly ones at the expense of patients. He also proposed that the recommendation include a call for CMS to study the issue. This proposal was seconded and ACBSCT members unanimously agreed to craft a recommendation for consideration and a possible vote by the end of the meeting.

Council member Susan Stayn, J.D., asked whether, given the amount of expertise on the ACBSCT, there would be a way to solicit comments on the issue and submit them to CMS. Mr. Walsh responded that this might require a full meeting of the council and a formal vote. Dr. Schriber noted that the council had recommended in 2010 and 2015 that stem cells be treated the way solid organs are for payment purposes but that no change had occurred and asked why CMS has not addressed this issue.

Comment

Doug Rizzo, M.D., said that his organization, the Center for International Blood and Marrow Transplantation Research (CIBMTR) at the Medical College of Wisconsin, collects outcomes data and believes CMS would find it difficult to study various components of a bundled payment. He also pointed out that bundling makes it hard to understand different products and donor types and that all products are different and act in different ways. Payment policy might have a broader impact on the decision making level and at the center level, he added. Assigning a code for the product and separate codes for other services could have a major impact on the development of products and services, including cord blood banks. He asked, therefore, whether one code provide enough data to consider usage trends in the future.

Karen Ballen, M.D., of Massachusetts General Hospital, who was a presenter during the meeting, said that, although we should be moving toward outpatient transplants, bundling could encourage practitioners to keep such transplants in the inpatient setting (because the payment rate is higher), which would make care more expensive.

Dr. McInnes pointed out that if the 15,267 payment for 2017 is too low, physicians have the option of doing an inpatient bone marrow transplant, so this has no effect on the inpatient payment systems for which the payment rate is in the tens of thousands of dollars. Dr. Rizzo said there are two things to consider: one is the current drive is to motivate centers to do outpatient transplants, which are safer and, in any case, the cost of getting a donor is the same for in and

outpatient transplants. Currently, however, to have a potential outpatient become an inpatient instead to receive treatment is not cost-effective. The second consideration is that bundling services into one code does not permit CMS to understand differences between different product types and different donors. As a result, assigning only one code to all transplants will not help CMS understand cost trends in the future.

Dr. Schriber also said that not making payment for donor acquisition independent of product costs shifts practitioners to more expensive care and creates disincentives for outpatient transplant procedures, which are safer.

Dr. McCullough said that, in short, the low payments could deter people from getting transplants, especially unrelated or cord blood transplants, and would steer the use of certain products over others, driven by cost rather than patient outcomes.

ACBSCT Update on Medicare Reimbursement Initiatives

Michael Boo, J.D.
National Marrow Donor Program

Mr. Boo began by saying that many of the Medicare payment issues that affect outpatient stem cell treatment also apply on the inpatient side and that the NMDP has reviewed the rules, commented and encouraged others to comment on them. He reviewed ACBSCT's previous reimbursement recommendations:

- Recommendation 11, issued in 2010, calling for Medicare reimbursement for acquisition of blood, marrow, and cord blood products for hematopoietic transplantation on a cost basis similar to reimbursement for solid organ transplantation graft acquisition.
- Recommendation 27, issued in 2015, calling for the HHS secretary to encourage CMS to reimburse the acquisition of blood stem cells, bone marrow, or umbilical cord blood products for HSCT on a cost basis consistent with CMS guidelines for organ transplants.

In the payer coverage analysis summary he provided, Mr. Boo noted that Medicare coverage has grown by 3 percent per year (as of the first quarter of 2015), but that coverage of procedures is limited and lags behind the current state of the science and provides inadequate reimbursement. The growth in the number of older patients being treated by transplant centers from 5 percent in 2005 to 25 percent in 2015 reflects the increasing ability to transplant these patients. By contrast, Medicaid coverage increased by 31 percent in 2015 and, although the types of coverage it provides is similar to Medicare's, unlike that program, its complex coverage rules are not public. Each state administers the program differently, the search for stem cell transplant donors is not well covered and most states do not provide adequate coverage. Full, private insurance offers the best benefits and end-to-end coverage with most indications covered, and provides travel and lodging benefits. Most of this coverage information is made public. Self-insured and individual coverage may not be reported or reported accurately and provide limited coverage and impose high out-of-pocket costs.

In reporting on the payment landscape, Mr. Boo noted that commercial payers reimburse based on a negotiated-case-rate basis, and that contracting networks have standardized coverage and reimbursement. Under this system, transplant centers are responsible for ancillary (non-bundled)

costs and reinsurance and third-party administrators often further scrutinize coverage and reimbursement. However, the number of people covered under private insurance is dropping.

Government payers, on the other hand, administer DRG- (inpatient) or APC-based (outpatient) reimbursement for Medicare. Medicaid's reimbursement is based on case rate or deep discount to fee for service and, like Medicare, centers have no ability to pass on ancillary costs to the patient.

Mr. Boo pointed out that expanding insurance coverage significantly increases care utilization. For example, providing Medicare coverage for treatment of myelodisplastic syndrome (MDS) through CMS's Coverage with Evidence Development (CED) mechanism increased hematopoietic stem cell transplantation among Medicare patients older than 65 from less than 100 in 2009 to close to 350 in 2014.

CMS has expanded reimbursement for allogeneic HSCT to cover leukemia, aplastic anemia and severe combined immunodeficiency disease. Also covered, but only when treatment is through a CED, are multiple myeloma (MM), myelofibrosis and sickle cell disease.

However, reimbursement costs for outpatient transplants are inadequate, and even the proposed increased reimbursement of $15,267 for transplants — which would include the costs of donor search and acquisition — are far lower than the existing DRG payment rates for inpatient treatment, which range from $22,453 for autologous transplants without major complications or comorbidity to $64,217 for allogeneic transplants. The payment disparity offers providers an incentive to use the inpatient — most expensive — setting, rather than the more efficient and economical outpatient setting to conduct transplants.

The fact that 124 of 562 transplant centers do not include transplant costs on their cost reports is reducing Medicare reimbursement rates because these data are used to determine average costs, and no adjustment is made to reflect zero reporting. The reporting rate has improved from 38 percent in 2007 to 79 percent in 2015. However, the actual reimbursement rate drops even further because CMS misapplies a discounting factor it has imposed on blood products.

An examination of bone marrow or peripheral blood costs revealed that, although the mean organ acquisition charges reported in inpatient hospital claims for allogenic stem cell costs are $51,727, the current inpatient payment system rate is only $62,245, which means hospitals lose money even before accounting for other expenses. This is especially true of cord blood because often two units are used to treat adults. As a result, hospitals are deciding not to offer HSCT to Medicare patients.

Boo recommended that the costs associated with acquisition of bone marrow and peripheral stem cell donors be treated the way CMS deals with kidney donors for purposes of transplant center reimbursement, not least because both types of donations entail similar associated services: tissue typing, donor evaluation, organ excision, operating room/ancillary services, as well as preservation, registry, transportation, and lab services costs. Currently, CMS handles reimbursement for these types of donations quite differently. Kidney acquisition from living donors is addressed separately from the DRG, and the hospital is compensated for reasonable expenses. HSCT, however, is treated within the DRG.

Mr. Boo maintains that the current CMS inpatient payment system would permit the adoption of parallel living donor policies, but transplant centers would develop a standard reflecting the average cost.

The proposed OPPS rule for 2017 calls for the outpatient HSCT (CPT 38240) to be moved into a new C-APC, and all costs submitted on the claim would be combined and averaged with other outpatient HSCT claims rather than being diluted by other, lower-cost services in a non-comprehensive APC. The new C-APC methodology will allow for upward adjustment based on cost reporting practices, but the higher payment still fails to reflect total acquisition costs or other costs of the procedure.

Mr. Boo pointed out that although the impact on patients will be a great increase in access to HSCT transplants among patients age 65 and older, the actual number will be small, especially compared with those who receive cornea or kidney transplants. In terms of costs, the per-member/per-month costs of transplants would be under $1.50.

Comment

Dr. Kamani asked, whether, given that many states have advisory boards that consider accepting pass-through costs, it would be an option to pursue the reimbursement issue at that level. Mr. Boo responded that the National Marrow Donor Program is looking into the 10 states with the largest Medicaid populations to increase coverage or payments. He pointed out that 50 percent of children who receive transplants are on Medicaid.

In response to a question about whether CMS covers reimbursement for stem cell treatment of multiple myelomas in tandem with other diseases with similar characteristics, Dr. Horowitz said that CMS treats this disease separately and specifically in terms of treatment. Cheryl Gilbreath, an analyst with CMS's Coverage and Analysis Group, said that a clinical CED trial of HSCT for multiple myelomas through allogeneic transplantation has been approved and is being conducted at the Medical College of Wisconsin. However, CMS has not been approached formally about reimbursement for tandem transplants or, regarding the question Dr. Giralt raised earlier about the potential for reimbursement for subsequent transplants involving one patient within a certain time period due to graft failure. CMS welcomes the submission of literature on this topic that it can consider and CMS contractors can consider some requests on a case-by-case basis.

Dr. Kamani suggested that there is a lack of engagement with CMS to indicate how the stem cell transplantation field has moved forward. He urged ACBSCT and the entire stem cell community to do this.

Another commenter mentioned that there are efforts to get broader individual stem cell transplant trials for multiple myelomas, myelofibrosis and sickle cell and that the sickle cell CED was as approved quickly because a biologic assignment trial had already been in process and it fit all of the requirements but it does not cover most people who have sickle cell disease.

Shelley Grant, branch chief for HRSA's Division of Transplantation, pointed out that ACBSCT based its decision to revive the 2010 and 2015 recommendations on reimbursement because of new membership on the council and in HHS, including Sec. Sylvia Burwell, who brings to the position new perspectives and ways of doing things. The secretary is routing such

recommendations through various agencies for review and is engaging CMS and other agencies, which is part of the reason that Ms. Gilbreath participated in this meeting.

Dr. Schriber asked whether ACBSCT should issue a recommendation that outpatient transplants be covered at the same rate as inpatient transplants since the procedures and associated services and costs are identical. He also asked whether stem cell transplants are included in the National Cancer Institute's Cancer Moonshot 2020 program, pointing out that, in addition to developing new cures, efforts should be made to educate the public on and foster the use of cutting-edge therapies that are already in use. Mr. Boo said that these transplants are not part of the Moonshot program, but that there are efforts to look into this.

Update on CIBMTR's Response to CMS's Coverage with Evidence Development (CED) for Blood Stem Cell Transplantation Indications

Doug Rizzo, M.D., M.S.
Center for International Blood and Marrow Transplant Research

CIBMTR operates the Stem Cell Therapeutic Outcomes Database (SCTOD) component of the C.W. Bill Young Cell Transplantation Program. The Medical College of Wisconsin was awarded the SCTOD contract; CIBMTR is a center within the college and represents a research collaboration between the NMDP/Be The Match and the Medical College of Wisconsin. Dr. Rizzo explained that he is project director for SCTOD.

He pointed out that CMS decisions on Medicare coverage often influence private insurers' and Medicaid programs' policies, and the agency's national coverage determinations (NCD) can specifically mandate or prohibit coverage for specific procedures in specific indications. If CMS does not issue a pertinent NCD, decisions are made by local Medicare Administrative Contractors, which often results in a no-coverage decision. Standard Medicare does not allow for prior authorization — advance approval for a procedure. These policies have posed an access barrier for patients with indications that are not on the covered list.

Allogeneic hematopoietic stem cell transplantation is the only curative therapy for patients with MDS, but, historically, Medicare patients older than 64 have historically not been covered for HSCT.

On August 4, 2010, CMS established coverage for HSCT to treat MDS through a CED. In December of 2010, CMS approved a CIBMTR study comparing outcomes of patients between the ages of 55-64 versus patients who are older than 64.

The MDS study permitted a great increase in the number of Medicare patients who received HSCT for MDS. The study is designed to provide responses to three questions:

- Do Medicare beneficiaries who receive HSCT have improved outcomes compared to those who do not?
- Prospectively, in Medicare beneficiaries with MDS who receive HSCT, how do International Prognostic Scoring System score, patient age, cytopenias, and comorbidities predict outcomes?

- Also, prospectively, what treatment facility characteristics predict meaningful clinical outcomes in these patients?

The study population consists of patients older than 64 or younger than 65 years old and a Medicare beneficiary, compared with a cohort of patients age 55-64. All have an MDS and related-disorder diagnosis and are eligible to receive an allogeneic HSCT from a human leukocyte antigen (HLA)-identical sibling or unrelated donor in a U.S. transplant center and are eligible for HSCT according to local institutional practices. Outcomes to be studied consist of 100-day mortality as the primary outcome and secondary outcomes of acute or chronic graft-versus-host disease (GVHD), relapse/progression, disease-free survival, overall survival and prognostic value of patient and disease characteristics on the outcome of HSCT.

The hypothesis being tested is that 100-day mortality among the 65 and older cohort is not significantly higher than in the 55-64 age group (20 percent).

Since the CED was approved, the number of allogenic HSCTs for patients older than 64 has increased four-fold and no differences in 100-day mortality or overall survival have been detected between the over-64 and 55-64 age groups. These findings led the researchers to conclude through observational study that age alone should not be a determinant for allogeneic HSCT eligibility.

A biologic assignment trail conducted by the Bone Marrow Transplantation Clinical Trials Network (BMT CTN; BMT CTN 1102) is also underway to compare HCST with best supportive care in patients aged 50-75. The results of this trial will not be available until mid-2020.

CIBMTR is conducting another clinical trial, the results of which CMS can use to examine whether to continue prohibiting coverage of allogeneic HSCT for multiple myeloma and continue remaining silent on HSCT for sickle cell disease and myelofibrosis. These policies have resulted in no Medicare reimbursement for allogeneic HSCT in myeloma and variable coverage for allogeneic HSCT for sickle cell disease and myelofibrosis nationwide. In 2015, NMDP, CIBMTR and the American Society for Blood and Marrow Transplantation petitioned CMS to consider covering these diseases, On January 27, 2016, CMS issued an NCD to cover allogeneic HSCT for some beneficiaries under its CED mechanism. This treatment only will be reimbursed for patients who are enrolled in the clinical trial.

Eligible patients have stage II or III (Durie-Salmon or IPSS) symptomatic multiple myeloma, intermediate-2 or high Dynamic International Prognostic Scoring System-plus score primary or secondary myelofibrosis or severe, symptomatic sickle cell disease.

The trial must be prospective, have as its principal objective to test whether allogeneic HSCT improves beneficiaries' health outcomes (no pathogenesis or toxicity studies) and compare survival with patients who have non-allogeneic HSCT therapy. The study must also control for selection bias and potential confounding by specific prognostic factors and address GVHD and transplant-related adverse events. And the three different diseases require three different studies.

Dr. Rizzo noted that, in some areas, Medicare had been covering HSCTs for sickle cell disease and myelofibrosis but now is not because of the CED, so there is urgency to proceed so that the path to transplantation is not interrupted for affected patients.

The sickle cell CED is BMT CTN 1503 Bone Marrow Transplants to Standard of Care for Adolescents and Young Adults with Sickle Cell Disease STRIDE2. CMS determined on June 14, 2016 that the study fulfills the national coverage determination criteria. Protocol activation for the study, in which 44 centers are expected to participate, is expected to begin in late September or early October.

The CED for myelofibrosis will compare the five-year survival probabilities from DIPSS assessment between allogeneic HSCT recipients and ruxolitinib/best supportive care. It involves the targeted accrual of 650 allogeneic HSCT recipients, about 225 of whom will be receiving myeloablative conditioning. The non-HSCT historical control cohort will consist of about 2,400 patients and there will be a descriptive haplo-identical donor cohort. [Note: During the comment period, Dr. Rizzo noted that, in the slide headed "CED for Myelofibrosis" the first sub-bullet under "HLA-Matched Donor HCT Study" should read, not "6/6 HLA-matched related donor" but "6/6 HLA-matched related and unrelated donor."]

The CED for myelofibrosis will focus on primary myelofibrosis or post-essential thrombocythemia/polycythemia vera with a DIPSS assessment of intermediate-2 or high-risk disease and patients must be age 55 or older at the time of DIPSS assessment. This will be an HLA-matched donor HSCT study involving a 6/6 HLA-matched, related donor, using peripheral blood stem cells and bone marrow. All conditioning regimen intensities and GVHD prophylaxis regimens will be permitted. The draft protocol for this trial is in the final stages of preparation.

The CED for multiple myeloma is designed to prospectively determine the outcomes of allogeneic HSCT for multiple myeloma in Medicare beneficiaries at or over the age of 65, compared with patients in this age group who underwent autologous HSCT for similar-risk multiple myeloma from 2010 through 2015. The study is designed to prospectively determine disease- or patient-related factors that predict the outcomes of allogeneic HSCT for multiple myeloma in Medicare beneficiaries. The draft protocol for this study should be finalized by the end of the end of 2016.

Comment

Dr. Giralt asked whether CIBMTR consults with CMS when designing its studies. Dr. Rizzo explained that the center designs them and then submits the proposed study to CMS for review and that the agency provides good specifications on what it expects the study to accomplish.

Dr. Rizzo also pointed out that the MDS project is an observational study to examine transplant outcomes between two age groups and compare transplant and non-transplant outcomes.

Dr. Giralt asked whether CMS will allow the MDS project to continue until the BMT CTN 1102 study has been completed. Dr. Rizzo said that the MDS study may have provided enough data for CMS to make a coverage decision on HSCT for MDS. Drs. Giralt and Schriber expressed concern that, if the MDS study is discontinued without a coverage decision, patients with MDS will not have access to HSCT therapy. They proposed that a recommendation be crafted and submitted to CMS to request that the study continue or to otherwise allow continued accrual of patients with MDS who could receive HSCT. At Mr. Walsh's request, Dr. Giralt agreed to draft the recommendation for a council vote during the new business section of the meeting.

Dr. Kamani explained that he had presented data to show that children with severe sickle cell disease who received transplants from related donors was an acceptable standard of treatment. He is concerned that if the sickle cell CED causes CMS to deny coverage until a determination of coverage is reached, Medicaid may follow Medicare's lead, as it often does, leading to a denial of Medicaid coverage to this group of patients and that it might be necessary to develop a non-transplant cohort to develop a study. Dr. Walters noted that CEDs are welcome but they can be restrictive in this way. He asked whether there are ways to develop non-transplant cohorts for rare diseases that would be funded by CMS (but then added that the answer is probably no).

Trends in Sources Used for Blood Stem Cell Transplantation

Mary Horowitz, M.D., M.S.
Center for International Blood and Marrow Transplant Research

Dr. Horowitz began by saying that everyone has a donor and that transplants are increasing by 3 percent per year because outcomes are improving and indicators are increasing, particularly MDS, follicular lymphoma and myeloma. The age range for transplants is also expanding for both autologous and allogeneic transplants. Donor availability is expanding as well. There has also been dramatic growth in use of unrelated donor HSCTs, in patients over the age of 50, supported by NMDP.

In terms of donor type, HLA-identical siblings — which is the gold standard — has been rising more significantly since 2003 and more steeply since 2008. Suitable donors provide HSCs that exhibit durable engraftment, good immunologic recovery and acceptable risk of GVHD. But HLA-identical sibling donors are available for only about 30 percent of transplant candidates. There are about 28 million unrelated bone marrow donors available through NMDP or Beat the Match. There are 74 stem cell donor registries from 53 countries.

The top 100 Caucasian A, B, C, and DRB1 high-resolution haplotypes have frequencies of less than 8 percent and most are under 1 percent. Extensive HLA diversity is important because it ensures protection from a broad range of organisms but frequencies of HLA types varies among different populations.

Dr. Horowitz noted that the one-year survival rate after HSCT in the United States in a 2016 center-specific outcomes analysis does not differ drastically among related and unrelated donors, ranging from 65 percent to 67 percent for unrelated donors from 2012 to 2014 to 72 percent to 73 percent for related donors, due to better matching. But success is as low as 10 percent among some ethnic groups. The influence of HLA match on survival after unrelated donor HSCT was similar for 8/8 and 7/8 match but more significant for 6/8 match. Research has shown no difference between antigen and allele-level matching.

An examination of the number of transplants from matched related and matched unrelated donor donors by race in 2010 and 2015 showed that Caucasian recipients outpaced African-Americans by far. African-American received less than 10 percent of all U.S. transplants even though they represent 30 percent of the population. The number of matched unrelated marrow transplants among African-Americans increased most sharply in 2015 compared with 2010. Transplants from matched related donors increased slightly. Transplants involving mismatched unrelated donations also increased significantly remained the lowest overall.

Dr. Horowitz noted that, in 2001, the number of patients receiving peripheral blood transplants began outpacing bone marrow transplants and, by 2015 had reached a four-fold increase, in part because early results showed better results and a lower rate of relapse. However, at the five-year mark, bone marrow recipients had improved outcomes in terms of quality of life, psychological wellbeing and GVHD symptoms.

However, a 2012 randomized trial of unrelated donor bone marrow versus peripheral blood transplantations for hematologic malignancies showed similar survival rates, disease-free survival and transplant-related mortality (TRM). Bone marrow had a higher rate of graft failure but peripheral blood had a higher rate of chronic GVHD.

At five years after HSCT, recipients of donor bone marrow were more likely to have better psychological wellbeing, less burdensome GVHD symptoms and were 50 percent more likely to return to work than peripheral blood recipients. Both recipient groups had similar survival, relapse and TRM rates. However, although long-term bone marrow outcomes were better, peripheral blood is still being used for at least 70 percent of unrelated donor transplants.

Dr. Horowitz also noted that patients without an adult donor may benefit from treatment from banked umbilical cord blood, which is immediately available; this is important for patients with aggressive disease. She also pointed out that cord blood poses no risk to the donor and allows more HLA-mismatch with lower risk of GVHD. Multiple studies have also shown that cord blood transplantation can establish durable hematopoiesis, have potent graft-versus-tumor effects and lead to successful transplant outcomes in a variety of malignant and non-malignant diseases in adults and children. The major limitation to cord blood transplantation is the small number of cells in each unit, which slows hematopoietic and immune recovery and can result in graft failure. Possible solutions include selecting large units, double cord transplantation — which is expensive, however — and expansion and homing techniques, which are currently being developed, but often require two units.

A new alternative may be the use of haplo-identical transplants, using T-depleted peripheral blood grafts, which has been done successfully in China with intensive immune suppression. Very few of these transplants have been done in the United States until 2010 and there are no U.S. Food and Drug Administration (FDA) approved CD34 selection or T-depletion devices. Johns Hopkins is using post-transplant cyclophosphamide to wipe out allogeneic-reactive cells and this approach has sparked interest.

Dr. Horowitz ended by noting that only half — 8,000 — of the 16,000 to 20,000 people in the United States who could benefit from allogeneic HSCTs receive them and stressed again that "everyone has a donor." She also noted that all donors (8/8, 7/8, adult, haplo, and cord) produce outcomes in the same range — the maximum differences in survival, compared to the 8/8 adult donor, are in the range of 10 percent to 15 percent. She also emphasized that donor availability cannot fully account for differences in access to HSCT in diverse ethnic and racial groups.

Comment

The question was asked why more peripheral blood transplants are being done in the face of evidence that bone marrow has better outcomes. Dr. Horowitz explained that early outcomes for peripheral blood were better and that the comparison results can be hard to track because

peripheral blood stem cell transplant recipients are coming to the hospital with negative longer-term outcomes individually and are temporally dispersed. Many physicians may also not want to believe that bone marrow is better because it is harder to procure, both practically and logistically, and the foundation for the Accreditation of Cellular Therapy requires that it be done by a bone marrow transplant specialist. Bone marrow also does not engraft as quickly as peripheral blood stem cells. There may also be a knowledge deficit among physicians about these longer-term outcomes.

Economic and geographic barriers exist as well. Karen Dodson of NMDP mentioned that 40 percent of donors must travel long distances to meet collection dates and types of donations requested. This is in part because not all transplant centers procure bone marrow but many would like to expand to be able to offer more services. Dr. Schriber suggested that more large centers should be encouraged to procure marrow; that currently, this burden now falls to many smaller centers.

Dr. Giralt suggested that ACBSCT write a recommendation to suggest to HHS Secretary Burwell that steps be taken to educate physicians on the latest bone marrow versus peripheral blood stem cell outcomes and allow other physicians, such as orthopedists and internists to procure bone marrow. Mr. Walsh pointed out that it might be more efficient and logical to take let the council's workgroup on access issues, which the council plans to revive, take up this issue.

The Future of Cord Blood as a Source for Hematopoietic Blood Stem Cell Transplantation

(Various aspects of this topic were covered by the following three presenters)

Update on Previous Cord Blood Banking Demonstration Projects

Karen Dodson
National Marrow Donor Program

Ms. Dodson described cord blood collection projects that have been started over the past three years. The projects are designed to expand the diversity of cord blood units, provide funding to support start-up costs for expansion in existing or new collection hospitals and promote the collection of high-quality cord blood.

The projects' year-one (FY 2014) goal of recruiting 1,600 or more cord blood units from minority donors at various centers proved to be more challenging than expected because of the time needed to start up collection sites, staff them and provide staff training. As a result, in the first year, 505 minority cord blood units were collected, 308 of which were donated by African-Americans. Efforts to meet the original goal continued in year two. In year three, HRSA provided $738,409 in grants and NMDP's "Be the Match" program provided a grant of $500,000 to incentivize the collection of total nucleated cells (TNC). Collections as of July 2016 are still short of funded goals (331 cord blood units collected versus 1,327 projected and 127 high-TNC units versus 553 projected) because starting collection centers in new delivery areas takes time, Ms. Dodson explained.

A strategy has been rolled out, targeting obstetricians and other labor and delivery staff to educate them on the importance of collecting high-TNC units. Many are unaware that most cord

blood units are discarded because they have low cell volume. To address this, a competitive "Volume is Vital Campaign" ran in August and September 2016, which included hospitals and cord blood banks in Georgia and Texas that received third-year grants to stress staff's roles in ensuring patients' transplant success. Success will be measured by comparing pre-campaign collection volumes to collections completed during the campaign. Promotional posters and pocket cards have been produced with images and text to remind staff of the goal and of the patients cord blood can benefits.

Year four (FY 2017) of the collection project will involve new and existing hospitals and the emphasis will remain on increasing the diversity of the inventory on the registry. There is particular interest in high-TNC unit collection but no specific incentives for this will be offered. HRSA has committed $950,000 for cord blood unit collections. Grants will be announced by Sept. 26, 2019.

Comment

Dr. McCullough asked what the approximately $1.2 million in funding in the third year would be used for. Ms. Dodson explained that it would go toward cord blood collections but that hospitals would also use it to fund the startup of new collection centers and ramp-up costs for existing ones to provide staff, training, increase collection hours, etc.

Another participant inquired about the density of African-American cord blood. Ms. Dodson explained that many of these units and those in Asian cord blood have lower TNC volumes. Ms. Grant explained that the strategy behind these projects also incorporates an "every drop counts" theme, to encourage a high collection rate because up to 95 percent of units from these donations may be discarded because they do not have high TNC volumes. What's needed to achieve this high collection rate is marketing, transportation, and promotion, not just money, she said.

Trend Data and Cost Models in Cord Blood Banking

Michael Boo, J.D.
National Marrow Donor Program

Mr. Boo began by explaining that the updated data he presented does not differ much from what had been presented previously, but his presentation was designed to remind attendees that it is available and a reminder of what a high-quality cord blood unit is in the context of achieving collection diversity. He noted that growth in the number of unrelated donor transplants supported by NMDP in the United States and abroad has been fairly flat since 2013 at a little under 6,500 in 2015 with the majority consisting of peripheral blood transplants. He showed a pie chart slide indicating that peripheral blood represents 65 percent of transplants, followed by bone marrow at 19 percent and umbilical cord blood at 16 percent. Cord blood shipments and transplants increased slightly in 2015 but the overall trend is lower, with shipments dropping from nearly 1,700 in 2011 to about 1,400 in 2015. Transplants have dropped from a high of 1,200 in 2012 to well under 1,000 in 2014 with a slight rise in 2015 to about 1,000. Cord blood transplants have decreased by 13 percent from 2015 to this point in 2016. Most of the units taken from the NCBI are high-volume; the registry a high number of small-volume units in inventory.

Mr. Boo noted that, in terms of inventory growth from minority cord blood sources from 2010 to 2015, almost 76 percent of units in the inventory have a TNC below 150. From 2005 to 2015, far more high-TNC units —TNC 150 and above — have been collected and significantly more have been shipped from Caucasian than from minority donors. Mr. Boo said advised that reallocating resources away from banking small units to increasing collections increases high-quality-unit collection.

In his discussion of NMDP's financial modeling for cord blood bank financing, Mr. Boo noted that funding these banks are being funded partly through government subsidies. He reported that cord blood banks are losing a great deal of money, ranging from net losses of $19,001,000 (-62 percent) in 2016 to a projected loss of $29,366,000 (-96 percent) in 2021. An increase in the use of cord blood is needed for the banks to reach break-even status.

Scientific Factors in Determining a Quality Cord Blood Unit

Karen Ballen, M.D.
Massachusetts General Hospital

Dr. Ballen began by reiterating the recommendations of the ACBSCT Work Group for Improving the Availability of High TNC Cord Blood Units for a Diverse Population, which Dr. Ballen and Ms. Hennessey presented at the March 2016 ACBSCT meeting. During that meeting, the Advisory Council voted to recommend that HRSA adopt a funding framework that incentivizes the collection of high-TNC units for a diverse population and that recognizes higher associated costs. The recommendation also recognizes the need to increase collections and that, in the quest for higher TNC units, fewer units overall will be banked.

Dr. Ballen also presented the recommendations of the Quality Committee of the NMDP Cord Blood Advisory Group, which was asked to define a high-quality umbilical cord blood unit and, after meeting several times over four months, approved and sent recommendations to Dr. McCullough in August 2016.

The group recommended a tiered TNC approach to reimbursement and offered as an example, Group 1: 90 <125 TNC (Minority) and 125 to <150 TNC (Caucasian); Group 2: 125 to <150 TNC (Minority) and 150 TNC or more (Caucasian); Group 3: 150 TNC or more (Minority) Details and reimbursement amounts would be defined by each bank's contract with HRSA.

The group also called for NCBI funding to be made available for unlicensed Investigational New Drug (IND) units that are banked by licensed banks and meet NCBI requirements when safety, quality, identity, purity and potency are not affected. Currently, NCBI funding is limited to licensed units issued by licensed banks. The group pointed out that the units would have been funded if they had been processed and banked by an unlicensed bank.

The group also recommended the implementation of a requirement for a minimum absolute viable post-processing CD34 of at or higher than 1.25×10^6 to align with specifications for FDA licensure. The group noted that CD34 is an important selection of a cord blood unit for transplant and that there is significant literature indicating the minimum level of CD34 in defining therapeutic benefit. The group also noted that test results are a required field for entry into the national registry and that this recommendation is in keeping with FDA guidance on unrelated

cord blood to treat patients with disorders affecting the hematopoietic system, issued March 2014.

Dr. Ballen also delivered a presentation on recognizing the considerations of transplant doctors when selecting the optimal umbilical cord blood unit for each patient. She noted that physicians take into account:

- Patients' age, weight, disease, disease status, protocol options and other donor choices;
- Cell dose as being one of the most important factors for survival;
- Tendency to choose larger cords, even in pediatrics cases and those involving double cords;
- Nucleated cell dose standard; and
- (Potentially) CD34 cell dose and CFU-GM.

Other factors include:

- HLA Match;
- HLA antibodies (which is controversial because the risk of graft failure can be higher);
- KIR match;
- Bank of origin (even though it is not clear whether there is evidence to indicate this is relevant);
- Infectious disease markers;
- Genetic screen; and
- Cord blood potency.

Comment

Dr. McCullough noted that much of the information in this presentation falls in the realm of offering advice to HRSA and providing more background in this context. The collection of more high-dose units from minorities will require higher collections generally, which will cost more. It will be up to HRSA to figure out how this is to be done. This does not necessarily require amending existing contracts, which can be difficult, but can be put into the contract process moving forward.

Ms. Grant asked whether Dr. Ballen believes that cell dose is a higher priority than HLA in determining which cord blood unit will result in the best quality outcome for the patient. Dr. Ballen said that different centers prioritize different criteria. Some want a smaller unit but a better match; others might look for lower TNC but a higher CD34 count. She pointed out that some Caucasian patients fared better after myeloablative cord blood transplants than African-American patients did, but when the latter group of patients received units with an adequate cell dose, no difference in outcomes was detected.

Dr. Delaney said that cord blood is considered primarily for patients who do not have suitable donors. She expressed concern that if only higher-volume units are banked, it could impede access. She called for efforts to educate physicians to refer patients to transplant centers. Cost and ease of transportation cannot be the reasons to refer patients. She also expressed concern that disposing of small units could waste those that would be useful for research, which is already

expensive and difficult to conduct. Dr. McCullough said that during the next year, studies will be done to address this issue.

Dr. Shpall reminded participants that cord blood usage has peaked and is declining due to cost, is difficult to transplant, takes longer and that recipients have poorer outcomes over time. She called for the establishment of centers of excellence that consist of centers that are willing to take on these more challenging patients. On the other hand, at the one-to-two-year post-transplant mark, many patients who are followed up are more active, stop using immune-suppression drugs and have better quality of life. If collections focus on higher TNC units, up to 95 percent of those collected could be discarded. A way needs to be found to distribute those. Dr. Giralt pointed out that in-patient haplo-transplant patients leave the hospital in half the time cord-blood recipients do.

Dr. Giralt pointed out that many people, including a large number of minority patients, do not have relatives they can draw on for haplo transplants.

Day Two, Wednesday, September 14, 2016
8:30 a.m.-12:30 p.m.

Differences in Utilization of Autologous Stem Cell Transplant by Ethnicity

Jeffrey Schriber, M.D.
Cancer Transplant Institute at the Virginia G. Piper Cancer Center

Dr. Schriber said that although much of the discussion has focused on allogeneic transplants, more autologous transplants are performed annually in the United States. He showed a chart indicating that these transplants had reached a high of about 1,2000 in 1996, dipped sharply to between 6,000 and 8,000 in 1998 when breast cancer "fell through" but have climbed since and remain well above allogeneic transplants, at least in part because they are most often used to treat multiple myelomas, non-Hodgkin's Lymphoma and Hodgkin's disease. These patients typically are older. The median age for MM patients is between 69 and 70.

Dr. Schriber has proposed doing a study to examine how many in the U.S. Hispanic population receive these transplants and how they fare and he plans to publish some findings on this topic through the American Society of Hematology.

Dr. Schriber also noted that multiple myeloma survival rates after autologous transplants improved steadily from 2000 through 2013. However, although African-Americans are more likely than other ethnic groups to develop this disease, the number of people who receive autologous transplants is far fewer than Caucasians across all diseases. This cannot be attributed to outcomes, all of which — non-relapse mortality, relapse, progression-free and overall survival — remain similar for those in both groups who receive these transplants for multiple myelomas, including males and females, a March 2010 study indicates. The rate of these transplants is lower for other ethnic groups as well.

Historically, many recipients have been young but the number of older multiple myeloma patients receiving this treatment is on the rise, a study conducted in April 2015 indicates, although the data do not capture all transplant activity or reasons for differences in this activity.

Comment

Dr. Schriber asked why autologous transplants are underused among minorities in the United States and why deaths are occurring in these populations. (Multiple myeloma is not considered curable but progress is being made toward this end.)

Dr. Giralt said that three of 10 patients with multiple myeloma never hear about the transplant option, and others are not receptive because they fear the treatment is too toxic or that they are too old. As a result, many are being referred in late stages of the disease if at all. Oncologists have knowledge gaps about the science and their failure to refer is affecting African-Americans more than Caucasians. However, this group is getting allogeneic transplants when they cannot find a donor, so progress in education on some fronts has been made. It was also suggested that internists, general practitioners and various professional medical groups could be educated about these transplant opportunities.

Ms. Stayn and Dr. Delaney suggested that clinicians and patients with non-malignancies and relatively rare conditions who could benefit from this therapy should be educated as well. Many of these patients are never referred for treatment.

Dr. Giralt mentioned that many potential recipients in this group have the bronze insurance plans through the Affordable Care Act (ACA), which offers very narrow coverage and often little to no access to transplant centers. Mr. Walsh said that CMS makes Medicare decisions and that there will be opportunities to discuss this with representatives who could attend meetings.

Dr. Schriber pointed out another issue: according to Medicare, much of the coverage would have to be provided by Medicaid whose policies are administered by the states, each of which sets its own Medicaid policies.

Ms. Dodson said that the Office of Patient Advocacy and Single Point of Access portion of the Be the Match contract has conducted research on where potential transplant patients may be underrepresented and could provide potentially helpful data.

Ms. Grant said that it would help HRSA to approach CMS on the issue of ACA coverage if the advisory council lays out its practical concerns and issues in writing and that, although it is up to that agency to decide whether to respond, it has had “Aha! moments” when the issues are clearly explained.

Dr. McCullough said that this is the type of topic ACBSCT would address in two parts; physician education on transplant therapies and the pay issue, which it will focus on through its access workgroup. Dr. Giralt and Dr. Schriber agreed to co-chair the access workgroup.

Update on the National Institutes of Health’s Blood and Marrow Late Effects Consensus Conference

Minoo Battiwalla, M.D.
National Heart, Lung, and Blood Institute

Dr. Battiwalla described the results that were reported during NHLBI’s Late Effects Conference, which was held June 21-22, 2016. He noted that early post-transplantation outcomes have been

improving steadily among autologous and allogeneic transplant recipients, both nationally and internationally, with an estimated five-fold improvement in survival rates by 2030 if transplant rates remain stable. Relapse rates are declining as well.

However, the number of post-transplant complications or illnesses is rising as survival improves and they can be lethal. Forty percent of childhood cancer survivors have and may succumb to severe illnesses. Many are caused by the effects of conditioning regimens (chemotherapy or radiation) and include gonadal failure, cardiovascular, thyroid, and pulmonary failure, bone loss, second cancers, endocrine disorders and cataracts. Other complications include infection, GVHD, and immune dysfunction. Pre-existing or a genetic predisposition for iron overload is another factor. These late effects have an impact on all domains; physical, sexual, emotional, psycho-social and financial.

The cause of many of these complications is not clear; hypotheses include HSC exhaustion, the effects of aging or neurodegeneration. The lack of cross-disciplinary involvement — most observation is being done within the transplant community — in tracking and studying these complications may be making them hard to assess, Dr. Battiwalla noted. In addition, most studies are observational and there are data and statistical gaps. There are also few financial incentives to do so. Some studies have been conducted through narrow lenses (e.g., a focus on GVHD.) Long-term retrospective studies of late infections that develop two to 10 years after transplant are needed. Dr. Battiwalla referred to these studies as highly achievable "low-hanging fruit."

The estimates indicate a 20 percent decline in post-transplant survival rate over 20 years four to nine times the rate among the general population. The most frequent cause of expected and observable deaths for patients surviving six years or more post-transplant was solid tumors followed by infection. At 15 years after transplant, the mortality ratio was two-fold. However, the cause of mortality tends to be identified far less often at or after 10 years post-transplant, possibly due to the lack of follow-up by transplant centers.

The NIH Late Effects Initiative was conducted to define critical issues and barriers in the field to determine what affects post-transplant survival, set research priorities and create an effective organizational framework for the study of late effects. Working committees were formed to identify knowledge gaps, give evidence-based recommendations and set a research agenda to improve bone marrow transplant survivor monitoring and management. Work began in March 2015 with the formation of a steering committee, followed by a planning meeting in June, working committee teleconferences in August, working committee draft presentations in February 2016 and culminating in the Final NIH Consensus Conference at the National Cancer Institute in Gaithersburg, MD.

The working committees were instructed to focus on post-one-year survival in cases not covered by a chronic GVHD initiative that were unique to bone marrow transplants. The approach was multidisciplinary and involved cross fertilization (e.g., pediatric oncology and HIV expertise) with the understanding that unique problems in this field may lead to generalizable solutions. The working committees were divided into the following areas and, during the final conference, delivered recommendations in the following areas:

- Research methodology — including cohort establishment/expansion to study late effects, prioritization of data collection, and development of pre-/peri-/post-transplant bio specimen repositories.
- Health care delivery — ranging from delivery models, coverage, and cost issues to health care policy (e.g., ACA).
- Subsequent neoplasms — focusing on long-term studies to capture data on pre-/peri-/post-transplant exposures, banking tissue for study, assessing genetic risk actors, effects of non-transplant-related risk factors, and validating cancer interventions in transplant survivors.
- Immune dysregulation — including focus on identification of and possible prevention of late infections, types of immune reconstitution and prevention, such as vaccination approaches and the role of IVIG and other therapies.
- Cardiac, vascular, and metabolic issues and interventions—examination of causes and interventions for arterial disease and cardiac dysfunction. and evaluation of cardiovascular risk factors such as hypertension, hyperglycemia, and dyslipidemia. and sarcopenic obesity.
- Quality of life and psycho-social issues—focusing on establishing a registry for patient-reported outcomes, including those in underrepresented groups, designing and testing interventions that address extent of use, and costs of effects that diminish quality of life and evaluating integration of patient-centered outcome screening across HSCT survivorship programs

Dr. Battiwalla included in his PowerPoint presentation a detailed listing of each working committee's recommendations.

Other conference highlights included a discussion of the importance of improving centers' patient follow-up efforts to enhance health care delivery, a patient perspective panel, a funding discussion and a workshop for junior researchers on "Starting a Late Effects Program."

Plans to disseminate conference findings include publication of white papers in the journal *Biology of Blood and Marrow Transplantation*, an educational session at ASBMT and EBMT, patient outreach and coordination and alignment of recommendations with existing bone marrow transplant initiatives such as the Bone Marrow Transplantation Clinical Trials Network. Dr. Battiwalla said that he hopes the conference will stimulate funding discussions at the federal level with an intra-agency agreement between NHLBI and HRSA.

Comment

Dr. Giralt said that this is an important initiative but expressed concern that no mention was made of the fact that although most survivorship discussion has involved children and young adults many more patients age 65 and older are between five and seven years post-transplant with quality-of-life issues. He pointed out that many geriatric transplant survivors are becoming nonfunctional at the seven- to eight-year mark and asked whether the groups have addressed geriatric issues. Dr. Battiwalla said that they had not been specifically addressed and acknowledged that there could be specific issues associated with them.

Ms. Hennessey said it would be useful to tie the research back to original decision making about treatment options made at the time of diagnosis or original treatment plan — when parents are making such decisions for their children, for example. In such cases, the issue of sperm preservation, which can be a major quality-of-life issue, would be relevant. Dr. Battiwalla said that this was not an area of focus because it is not transplant-specific. Dr. Delaney said that, as a pediatric oncologist, she does focus on this issue because it can effect what type of treatment is pursued. She noted, however, that, by the time young patients reach transplant stage, they often have undergone radiation or chemotherapy, which, of course, often results in infertility. She added, however, that some post-transplant patients are fertile and that parents often raise this issue.

Dr. Schriber said that long-term follow-up is a major issue that could inform treatment options for peripheral and cord blood transplants as well. Dr. Battiwalla noted that having a survivorship program is a FACT quality standard.

ACBSCT member Manish Gandhi, M.D., said that without funding, the type of research Dr. Battiwalla is calling for will not be conducted. Transplant centers do not have the money to do long-term follow up or research. It will require effort beyond this community to move beyond a small amount of fragmented reporting. He said that the children's oncology group is able to do this large-scale because it has the funding and it should be done for other allogeneic transplant survivors as well.

One of the ACBSCT members pointed out that many African-Americans refuse to undergo such chemotherapy, radiation, and other such treatments because they are concerned about quality of life.

FDA Update on Licensure of Cord Blood Banks
Safa Karandish
Consumer Safety Officer
U.S. Food and Drug Administration

Dr. McCullough introduced Ms. Karandish as FDA's new liaison to ACBSCT. She provided a brief overview of regulations governing FDA's Biologics License Applications (BLA) and licensure compliance requirements. She also mentioned common questions cord blood banks have asked FDA about its regulatory requirements, most of which involve Current Good Manufacturing Practices (CGMP) requirements and the implementation of post-approval changes to approved products as part of products' life-cycle management.

She announced that FDA has approved seven cord blood bank BLAs, the latest of which was approved in September.

As part of its BLA review process, FDA conducts pre- and post-licensure inspections and is providing additional training for FDA inspectors and will, when possible, make a product reviewer available during inspections either in person or by phone.

FDA engages with stakeholders in meetings and attended an international cord blood symposium held in San Francisco in June, during which representatives provided an overview of BLA requirements and lessons learned. The agency also held a meeting with cord blood banks as a group to discuss general topics.

Robert Hartzman, M.D., director of the Bone Marrow Research Directorate at the Naval Medical Research Center, said that obtaining licensure is useful and that the process works but the cost involves is a major issue for many cord blood banks. He asked whether there was a more effective way to achieve the quality in products than through these requirements.

Dr. McCullough added that although "we love CGMPs," some of FDA's requirements are overly onerous and are not regulations a priori. He pointed out as examples, the agency's particle count in rooms and limited access requirements, referring to these as "overkill." He noted that FDA made these rules over time and can "unmake them." Ms. Karandish said that the FDA's regulatory framework is the basis on which it makes its decisions and requirements. She explained that, under FDA's regulatory requirements for HSCs, minimally manipulated, unrelated allogeneic products are regulated as biological drugs and, therefore, are subject to licensure or IND requirements and compliance with CGMPs. Licensure provides the necessary controls and quality assurance, she said, while acknowledging, however, that the licensure process is a learning experience. FDA is providing advice to cord blood banks on how to implement this process in the least burdensome way.

ACBSCT member Thomas Price, M.D., asked how many cord blood banks are not licensed but are "in the pipeline," and whether there is a specific date by which banks must achieve licensure. Ms. Karandish said she does not know how many banks nationally are not licensed but said there is no deadline for achieving licensure. She explained that when FDA implemented BLA and IND requirements the agency also acknowledged the public health need to ensure patient access to these products and respects HRSA's desire to increase the HLA diversity of banked units.

Dr. Shpall said that most licensed banks are prospectively licensed and that all other units are managed under an IND, "which is great for all 750,000 units that will not be licensed."

Joanie Hare, M.D. of the M.D. Anderson Cancer Center, asked Dr. Karandish to list the names of the seven licensed cord blood banks and asked whether any are small and/or private. Ms. Karandish said that they vary in size and listed (informally) five of them: New York Blood Center, Blood Works, Duke University, St. Louis, and Colorado, and said she could provide a full list of the seven upon request. Ms. Karandish confirmed that private cord blood banks are not subject to licensure but are subject to 1271 regulations and section 361 of the Public Health Service Act.

Mr. Boo said that NMDP has been gathering information from cord blood banks on the benefits and challenges of licensure in public for and has facilitated discussions with FDA.

Ms. Karandish said that FDA has published guidance on the BLA process that can provide helpful information on the agency's thinking but another participant said that only statute and regulations are binding, not FDA guidance, and asked whether the agency would consider other approaches banks may wish to take to meet CGMPs. Ms. Karandish said that cord blood banks can propose other ways to meet these requirements and that FDA would consider them.

Mr. Boo said that a survey NMDP conducted indicates that cord blood banks have taken a variety of approaches to obtaining licensure, some of which are more costly than others but that the process is inevitably expensive, both in terms of infrastructure and ongoing facility management, and that there is no "magic bullet" to address the costs. He said that the guidance

Ms. Karandish provided matches that which NMDP would provide to cord blood banks. Dr. Kamani noted that some cord blood banks have spent $1 million to meet FDA's biologic standards, but said the agency is willing to work with cord blood banks on this.

Dr. Schriber asked whether there is any evidence that products produced by licensed banks are better than those from unlicensed banks. Mr. Boo said that relatively few units have been available upon which to base a comparison but no particular benefits have been ascribed to licensed units. He pointed out, that other selection factors are usually more important to clinicians. Mr. Boo added that it could be argued that obtaining licensure could qualitatively prevent problems with units "on the edges of processing" and that banks have alluded to this.

Dr. Delaney said that, as a practitioner, she examines some factors related to improving patient outcomes, such as automated processes and accreditation, as well as a preference for U.S. banks out of convenience. She noted that licensure is not one of the factors she considers. In fact, she pointed out that products from licensed banks can be more expensive. As a result, "licensure can backfire." Dr. Shpall concurred, saying that units from licensed banks can be 10 percent more expensive than non-licensed ones.

It was pointed out that licensed banks are only reimbursed for licensed units whereas unlicensed banks are reimbursed for all units that meet HRSA's requirements. CAPT Greenwald said, however, that HRSA views licensure as an indicator of quality and that it strives to get good quality units to patients who need them. HRSA does not discuss outcomes, however — but leaves that up to FDA, she added. Ms. Grant referred attendees back to HRSA's three funding tiers of cord blood banks that CAPT Greenwald had described during her introductory remarks, reminding them that licensed banks are in Tier 1.

An online meeting participant, Phyllis Warkentin, M.D., chief medical officer of the Foundation for the Accreditation of Cellular Therapy, asked whether the council should be asking why six of the 13 HRSA-funded cord blood banks are not licensed. Ms. Grant said that within NCBI contracts, cord blood banks provide information annually on whether they are licensed or are making progress toward it and HRSA includes it in its annual report.

New Business

The ACBSCT voted on two recommendations that were discussed earlier in the meeting and during this part of the meeting.

The first recommendation, which the advisory council will ask HRSA to send to CMS, asks the agency to address what all members view to be the inadequate FY 2017 proposed Medicare outpatient payment rate for stem cell transplants, with a specific emphasis on the high costs of acquisition. During discussion of this recommendation, Dr. Giralt, who proposed and drafted it, expressed concern that the proposed payment is so low that it would cause physicians to avoid performing cord blood transplants in favor in favor of haplo-identical transplants.

Also discussed was the potential to ask CMS study the costs of all types of stem cell transplants and set specific Medicare codes for each to accurately reflect their specific costs but the advisory council decided that this could not be done in a timely manner and left open the possibility of making that suggestion at a later date. The council agreed to make its current recommendation narrower, focusing on the proposed payment alone, hoping CMS might address it fairly quickly.

One of the council members also noted that the period during which CMS would consider public comment on the Medicare outpatient payment rule for FY 2017 has expired but that the agency can choose to consider recommendations ACBSCT puts forward outside that timeframe.

The recommendation reads as follows:

Recommendation

The ACBSCT is concerned that the proposed outpatient C-APC 5244 payment rate of $15,267 is insufficient to cover costs of procurement from different stem cell sources. The proposed payment rate fails to recognize the different acquisition and treatment costs associated with different sources of HSCTs.

The ACBSCT recommends that distinct reimbursement rates be developed for different stem cell sources.

The Advisory Council voted unanimously to approve this recommendation.

The second recommendation asks the HHS secretary to take action to ensure that patients age 55 and older continue to have access to HSCT for MDS through an observational study of this treatment's efficacy, rather than ending the study or to use other avenues to do so and alludes to a related clinical trial being conducted to compare HSCT with best supportive care in middle-age-to-older patients, the results of which will not be released until mid-2020.

The recommendation reads as follows:

Recommendation

The ACBSCT has reviewed the outcomes presented by the Center for International Blood and Marrow Transplant Research (CIBMTR) at the American Society of Hematology meetings in December 2015 for data collected under CED protocol number CAG-00415N. These data (previously shared with CMS by CIBMTR) show increasing access and similar outcomes for recipients of allogeneic hematopoietic cell transplantation (HCT) for Myelodysplastic Syndrome (MDS) in age groups 55-64 and those 65 and older. CIBMTR has collected sufficient information in its observational study to address the relevant scientific questions outline in the Decision Memorandum of August 2010, once follow-up is complete. Results from the biologic assignment trail conducted by the BMT CTN (BMT CTN 1102) comparing HCT with best supportive care in patients aged 50-75 will not be available until mid-2020.

Based on data presented at ASH 2015 (Atallah, EA et al; Blood 126;195, 2015 (abstract)) and understanding that MDS is an established indication for transplantation among patients younger than age 65, and to ensure access to transplantation for Medicare beneficiaries continues, the ACBSCT recommends to the secretary of HHS that CMS take one of two courses of action with regard to this indication.

- Revise its current National Coverage Decision (NCD) to eliminate the requirement of a CED to specify MDS as a covered indication for HCT based on reported outcomes to date,

OR

- Authorize continuation of the CIBMTR observational study under CED, using standard data collection, to allow for continuing accrual of patients through the time of any relevant modification to the NCD based on the results of the BMT CTN trial.

We request that CMS ensure a mechanism for interim coverage of HCT for MDS during the National Coverage Analysis process for either course of action.

The Advisory Council voted unanimously to approve this recommendation.

In response to ACBSCT's decision to revive and provide staff to support two existing working groups and start a new one. The groups and a list of the members that have volunteered to serve on them* are listed below. (*Mr. Walsh will contact other potential members and ask workgroup co-chairs to nominate members as well.)

ACBSCT Working Groups

Access to Transplant Physician and Patient Education & Payment Issues

Co-Chairs: Jeffrey Schriber and Sergio Giralt
Joanie Hare
Helen Crawley-Austin
Elizabeth Shpall
Susan Stayn
Mark Walters
Michael Boo
Andrew Campbell

Scientific Factors of a Quality Cord Blood Unit

Chair: Elizabeth Shpall
Karen Dodson
Michael Boo

New Uses for Adult Blood Stem Cells and Birthing Tissue

Chair: Colleen Delaney
Robert Hartzman
Naynesh Kamani
Elizabeth Shpall
Joanie Hare

Ms. Grant said that she and Mr. Walsh would examine the charters for each of these working groups to help set the foundation for their work and provide guidance regarding what issues they could address. She offered as an example a question that could be asked of the Scientific Factors of a Quality Cord Blood Unit: whether its discussions would cover only units that are under contract to the NCBI program or the broader array of unit types — some of which are not under the NCBI contract — that would be collected under the C.W. Bill Young program.

Dr. McCullough noted that, although only ACBSCT members can chair working groups, members of the public can serve on them as well, and he invited anyone calling in to participate in them.

Dr. Schriber pointed out that the issue of why payments for inpatient stem cell transplants differ from outpatient transplants — since costs of the procedures and associated expenses are the same — was not addressed in this meeting or the prior one due to lack of time. He noted, however, that this issue has access implications and, therefore, could be taken up by that work group.

Dr. Schriber asked when new members will be appointed or people whose terms have expired will be told if their terms will be renewed. Mr. Walsh said expired terms will be extended until new members are appointed. Those are pending and there's no date scheduled for their appointment.

CAPT Greenwald thanked everyone in the room and specifically ACBSCT members' for their time, comments, energy, and their passion for caring for patients receiving transplantation.

Dr. McCullough thanked all who participated in and organized the meeting.

No public comments or questions were received during this part of the meeting.

Dr. McCullough adjourned the meeting at 12:40 p.m.

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