ADVISORY COUNCIL ON BLOOD STEM CELL TRANSPLANTATION

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

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One Bethesda Metro Center
Bethesda, Maryland 20814

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Monday, December 15

Mr. Remy Aronoff, Executive Secretary of the Advisory Council on Blood Stem Cell Transplantation (ACBSCT), called the meeting to order at 8:30 a.m. He then introduced Richard Durbin, who became Acting Director of the Division of Transplantation (DoT) after Dr. Jim Burdick retired in November. Mr. Aronoff then turned the floor over to Robert Baitty for a program update.

Status of the C.W. Bill Young Cell Transplantation Program & National Cord Blood Inventory

- *Robert Baitty, Director, Blood Stem Cell Transplantation Program*

Mr. Baitty began his presentation with an update on the status of the four large contracts that are the main components of the program: the Bone Marrow Coordinating Center (BMCC), the Cord Blood Coordinating Center (CBCC), the Office of Patient Advocacy/Single Point of Access (OPA/SPA), and the Stem Cell Therapeutic Outcomes Database (SCTOD). These contracts are performing well and have completed their 2-year base periods; the first of 4 possible option years were awarded for all contracts as of September. The Continuing Resolution funding for the program is $23.5 million, which exceeds the President's budget request by $800,000.

Mr. Baitty informed the Council that the number of transplants facilitated through the program was increasing sharply and that the program was on track to meet the goal of facilitating 4,500 transplants annually by 2010. In Fiscal Year (FY) 2008, the program facilitated 4,330 transplants, compared to 3,679 in FY 2007, an increase of 18 percent. Mr. Baitty noted that the goal for the program was established by the Health Resources and Services Administration (HRSA) and the Office of Management and Budget, with the involvement of the National Marrow Donor Program (NMDP) as the National Bone Marrow Donor Registry contractor. The baseline for that goal was 2,310 transplants facilitated in 2003.

Mr. Baitty stated that the number of transplants for minority patients was increasing more rapidly than for Caucasian patients. In FY 2008, the program facilitated 672 transplants for individuals of racial and ethnic minority backgrounds, exceeding the goal of 636 transplants by 2010.

The health outcome measure for the program is the 1-year post-transplant survival rate for standard risk patients. The survival rate is currently at 68 percent, a considerable increase from

the baseline of 62 percent in 2003. The goal for 2010 is 69 percent. Mr. Baitty stated that data for other aspects of the program show similar trends, with outcomes for unrelated donor transplants now approaching those of sibling transplants.

Mr. Baitty stated that adult donor recruitment levels were higher than ever, with about 400,000 donors recruited last year. Recruitment of Caucasians was at 97 percent of the goal for FY 2008. Recruitment for minorities exceeded the goals, reflecting targeted efforts to recruit in each of the minority population groups.

Mr. Baitty presented data on patients transplanted with cord blood units (CBU) and with adult grafts by race/ethnicity in FY 2008. Minority patients comprised nearly 30 percent of the 898 patients who received cord blood transplants, compared to about 12 percent of the patients who received adult grafts. Cord blood appears to be fulfilling the promise of extending a transplant option to groups that historically have had the greatest difficulty finding a well-matched adult donor.

Mr. Baitty noted that the Office of Patient Advocacy/Single Point Access organized a Marrow & Cord Blood Transplant Survivorship Summit in June 2008 and a Patient Advocacy in Cellular Therapy Symposium in September 2008. These meetings brought together advocacy groups and key stakeholders to address persistent barriers and burdens experienced by patients.

Turning to a discussion of the outcomes database, Mr. Baitty noted that data collection for all allogeneic transplants began in December 2007, and Stem Cell Therapeutics Outcomes Database (SCTOD) staff are in the process of planning the best approach to report transplant center-specific outcomes for both related-donor and unrelated-donor transplants. In September, the Center for International Blood & Marrow Transplant Research (CIBMTR) and the American Society of Blood & Marrow Transplantation held a forum to discuss issues involved in this analysis; a similar meeting will be conducted during the Tandem BMT meetings in February 2009. The FormsNet software that supports the database has been upgraded and is working well. The transition to CIBMTR providing outcome data to cord blood banks has been accomplished, though with some delay in reporting complete data to banks, particularly for transplants that were not facilitated through the Single Point of Access. Bi-weekly conference calls with banks, some transplant centers, CIBMTR and HRSA are being held to hasten remedies.

Mr. Baitty informed the Council that the National Cord Blood Inventory (NCBI) was operating under the Continuing Resolution at a level of $8.8 million, although the President's budget had requested $12 million for this program. As of November 2008, approximately 14,000 cord blood units were available through NCBI, with nearly 16,000 additional units to be collected with the funding provided to date. All banks are now collecting at a good pace, with more than 1,000 new NCBI units banked each month. There also has been a significant increase in the utilization of the NCBI units as the inventory grows. In FY 2008, 104 NCBI units were shipped for transplant, compared with only four units shipped in 2007. To date, there have been three funding cycles for NCBI cord blood banks (CBBs). The third cycle concluded in September with funding of LifeCord in Gainesville, Florida, which has a system for outreach to hospitals in Florida, Alabama, and Georgia with large numbers of African-American births. Mr. Baitty displayed a map showing the locations of NCBI banks in each cohort, as of September, 2008.

Mr. Baitty noted significant improvements in turn-around times from collection to listing of CBUs. Banking of qualified units from African-Americans remains the greatest challenge, with cell counts as the main difficulty. Potential solutions include reducing the cell count criteria for that population, which Mr. Baitty did not recommend because cell dose importantly affects transplant outcomes, or increasing efforts to obtain units from that population that meet the funding criteria. This will require more work, which banks should factor into their budgets and NCBI cost proposals.

Mr. Baitty stated that planning was underway for a fourth cohort this year, as well as continuation funding for banks that are performing well, and his office had begun planning for potential renewal of the existing contracts. He noted that the law limits funding for an individual bank to 3 years. However, the law permits extensions of a contract beyond 3 years if two conditions are met: 1) fewer than 150,000 units are available, and 2) there are no new applicants, or the new applicants are not sufficient to reach the goal of 150,000 units. Mr. Baitty noted that both conditions will be met this fiscal year, and his office was now exploring the best way to offer extensions to banks in the first cohort that are performing well. Once the principal options have been identified, input would be solicited, especially from the banks and from Council members. Mr. Baitty noted that there will not be sufficient time for the Council to vote on an official recommendation, but individual Council members will be able to offer suggestions.

Mr. Baitty provided an update on the Related Cord Blood Donor Demonstration Project, which was described by Randy Gale at the Council's first meeting. The project was launched in October 2008 and is coordinated by the National Marrow Donor Program (NMDP). Five NCBI banks chose to participate in this optional activity and have had their contracts amended to include a small amount of funding to collect and store these units; two private (family) banks with national reach have agreed to participate in the project, although they will not receive any funding. The OPA/SPA will be responsible for referring patients to the participating banks. In addition to collections from full siblings of patients, the legislation extends eligibility to all first-degree relatives, which could include parents. Recognizing that family cord blood transplants for parents have been extremely rare and that the degree of match in tissue type would be much lower than is possible with sibling transplants, HRSA has developed different eligibility requirements for siblings and parents. For sibling patients, the program requires diagnosis of a transplantable disease. If the designated patient is a parent, the program requires evidence of enrollment in an established protocol that would accept a haploidentical cord blood unit for transplant, as well as diagnosis of a transplantable disease. The Council will be involved in preparing a report that the Secretary will submit to Congress at the end of the 3-year project. The report will include a recommendation as to whether to continue this type of activity.

Mr. Baitty concluded his presentation by providing information on the Web site for the C. W. Bill Young Cell Transplantation Program (http://bloodcell.transplant.hrsa.gov/). He noted that the Web site now includes a page to help researchers contact banks that may make cord blood units available for research. This page was added in response to a suggestion made by the Council in its meeting (April, 2008).

Discussion

Dr. Bert Lubin noted that reports to Congress provide important information to justify continued support. He suggested that these reports should include information on transplants for non-malignant diseases, which are likely to increase, as well as information on cost savings and benefits of such transplants. He also noted that families who wish to donate cord blood do not always live near collection facilities.

Dr. Joanne Kurtzberg replied that NMDP's Cord Blood Committee was discussing a kit model that would enable interested mothers to donate to the public program. She added that the Foundation for the Accreditation of Cellular Therapy (FACT) recently approved an amendment to the standards that would allow accreditation with a kit model. Mr. Baitty noted that the program was interested in the possibility of using a remote kit-based model to expand the reach of the demonstration project.

Dr. Clive Callender acknowledged the positive work of the NMDP with minority populations. He asked what steps had been taken to include minority populations in non-malignant stem cell transplantation as well as tissues other than bone marrow and cord blood. Mr. Baitty replied that emerging uses of other cells were the purview of the National Institutes of Health and the Food and Drug Administration. The legislation for the HRSA program is limited to therapies that use cells from cord blood or bone marrow.

Tools Available to the Secretary of HHS for Implementation of ACBSCT Recommendations

- *Mark McGinnis, JD/MPH, Office of the General Counsel, Public Health Division, HHS*

Mr. McGinnis provided an overview of the role of the ACBSCT and discussed the Secretary's options for implementing recommendations submitted by the Council. He noted that this Council differed from most advisory committees because it was required by statute, rather than by Federal rule. He reviewed the Council's charter, which identifies the range of issues on which it is to advise the Secretary.

Once the Council submits a recommendation, the Secretary's response could include proposing legislation or shifting discretionary funds but almost always results in approval of the recommendation with implementation being the responsibility of the program.

Mr. McGinnis stated that the Council should not consider any topic to be off the table. The Council's role is to provide an expert opinion on issues that it considers important and relevant. Departmental staff are responsible for determining the legal, programmatic, or practical feasibility of implementing the Council's recommendations.

Mr. McGinnis cautioned the Council that recommendations requiring legislative changes are beyond the Secretary's direct authority, although he can advocate on behalf of the proposed legislation. Mr. McGinnis cautioned the Council about anti-lobbying restrictions. The Council's charter is limited to formal recommendations to the Secretary, although Council members are free to advocate individually as members of the public.

Mr. McGinnis outlined the Secretary's options if rulemaking is required. He noted that the rulemaking process could take several years from initial proposal to final regulation; but it usually is faster, and often better, than legislation. Rulemaking typically involves many parts of the Department, such as the Food and Drug Administration (FDA) or Centers for Medicare and Medicaid Services (CMS).

Discussion

Dr. Callender reiterated his concern about minorities being left out when it comes to successful stem cell transplantation. He felt the Council should be proactive about increasing minority participation. Mr. McGinnis noted that minority outreach was included in the legislation and the Council was making recommendations in that area. He encouraged the Council to be proactive in addressing this issue.

Workforce Issues in Blood and Marrow Transplantation

- *James L. Gajewski, MD, FACP, Professor of Medicine, Oregon Health and Science University; Chair, Reimbursement Committee ASBMT*

Dr. Gajewski noted that the Council had expressed a clear desire to expand the number of bone marrow and stem cell transplants. However, he cautioned that a shortage of providers at all levels of the health care workforce could make it necessary to contract, rather than expand, these services.

Dr. Gajewski described cyclical shifts in U.S. physician workforce concerns and policies. From the 1950s to the 1970s, concerns about physician shortages led to Federal funding to expand medical school capacity and enrollment. Around 1980, concerns about physician surpluses gave rise to Federal recommendations to limit the growth of physician supply. By 2000, there was renewed concern about shortages. Dr. Gajewski noted that this trend would have been noticed sooner if residencies had not been opened to international medical graduates in the 1990s.

A consensus is now emerging that physician shortages are likely. The Council on Graduate Medical Education (COGME) predicts a shortage of 100,000 physicians by 2020, even assuming a 30 percent increase in medical school enrollment.

Dr. Gajewski displayed a U.S. map showing areas that are currently experiencing shortages of primary care physicians. According to HRSA, 30 million people live in federally-designated shortage areas and lack access to basic medical services. The U.S. lags far behind many developed countries in terms of physicians per capita.

Dr. Gajewski outlined the workforce position of the Association of American Medical Colleges (AAMC):

- Expand US medical school enrollment by 30 percent by 2015
- Eliminate the caps on graduate medical education (GME) funding
- Expand the National Health Service Corps (NHSC) by 1,500 positions
- Increase the diversity of the medical school workforce

- Examine options for assessing medical schools outside of the U.S. for accreditation
- Encourage improved medical education in less-developed parts of the world.

Dr. Gajewski presented a graph illustrating the decline in per capita medical school enrollment since 1980. Even with a 30 percent increase in enrollment, the U.S. would not achieve the physician/population ratio of 1980. A 2005 survey found that only 24 percent of allopathic schools had definite plans to increase their first-year enrollment.

Factors driving physician demand include U.S. population growth, the aging of the population, and changing physician utilization rates, with those under age 45 using fewer services than those over 45. Dr. Gajewski noted that departmental and legislative decisions would be driven more by these larger societal considerations than by specialized issues, such as transplantation.

Dr. Gajewski outlined numerous factors impacting the supply of physicians:

- Time frames to change the supply or distribution of physician are lengthy due to years of education and training
- State funding for medical schools is contracting during the recession
- Significant shortfall in medical school slots
- Capped residency programs and restrictive Residency Review Committee requirements
- Medicare and Medicaid funding for GME is targeted for elimination
- Massive student indebtedness due to lack of scholarships
- Lack of a national planning system; limited Federal guidelines; and few fiscal incentives
- The aging physician workforce, retirement patterns, and lifestyle choices
- Physician attrition and burnout
- Increase of women in practice
- Changing practice patterns, with greater preference for outpatient practice and shorter work weeks
- Productivity changes
- Immigration policies have restricted the supply of international medical graduates in recent years

Specialty selection also impacts physician supply. Bone marrow and cord blood transplant require specialization in both internal medicine and oncology, with experience in an inpatient setting treating patients with multi-organ dysfunction. In recent years, however, internal medicine training has shifted to the ambulatory sector, which limits training to single-organ system problems.

Dr. Gajewski presented data on blood and marrow transplants (BMTs) reported to the CIBMTR and projected demand for physicians providing BMT services. He noted that pediatric growth was expected to remain stable, while adult growth would increase dramatically, particularly among elderly patients with co-morbidities. Dr. Gajewski stated that younger physicians are not trained to deal with the types of issues that these patients present.

Citing demographic data from membership records of the American Society for Blood and Marrow Transplantation (ASBMT) and the American Medical Association, Dr. Gajewski noted

that almost 30 percent of the specialists in hematology-oncology, immunology, and blood and marrow transplantation, and internal medicine are over age 55. These physicians cannot be expected to maintain the same level of productivity.

Addressing the impact of technology, Dr. Gajewski observed that physicians spend an increasing percentage of their time in non-patient care activities. Electronic medical record (EMR) systems are important, but they require physicians to spend additional time on data entry.

Dr. Gajewski dismissed the view that shortages could be addressed by increased use of nurse practitioners, physician assistants, hospitalists, and other clinicians. He pointed out that hospitals across the country are facing shortages of qualified nurses and other staff, and the average age of the nursing workforce is increasing. Hospitalists cannot integrate cancer/transplant management with other co-morbid diseases, and there is no methodology to pay physicians for supervising other physicians.

The increasing number of survivors presents additional burdens on medical systems. Dr. Gajewski stated that BMT physicians must be accountable for the care of patients with complications after transplant. Primary care physicians are in short supply and are overwhelmed caring for patients with single-organ system problems. Private hematology-oncology doctors focus primarily on administering chemotherapy to new patients, rather than caring for long-term patients with multi-organ dysfunction.

Dr. Gajewski emphasized that the 2020 BMT physician supply problem must be addressed now. Only one-third of the 246 transplant centers in the U.S. have a BMT fellowship program, and those programs have very few slots. Since it takes 3 to 5 years to add medical education capacity and 10 years to train new physicians, it will be 13 to 15 years to achieve a small, marginal increase in the number of BMT physicians.

Dr. Gajewski called for research to improve ASBMT's understanding of the BMT workforce. He recommended conducting a survey of members to update information on the composition of the workforce, combined with a survey of transplant centers to obtain information on staff BMT physicians.

Dr. Gajewski concluded by recommending several strategies to increase the future supply of BMT physicians:

- Support increases in U.S. medical school enrollment and graduation, and identify new funding sources.
- Support GME increases for internal medicine, pediatrics, and hematology-oncology.
- Revise internal medicine and pediatric residency curricula to ensure adequate training on inpatient multi-organ failures.
- Encourage BMT colleagues to become involved with medical education, including the education of internal medicine and pediatric residents.
- Increase the number of BMT training programs and training slots, and identify funding sources to support them.
- Retain active physicians longer.

- Encourage the development of creative care delivery systems for BMT patients that incorporate all health care professions.

Dr. Gajewski thanked the Council for its consideration.

Discussion

Dr. Rebecca Pentz asked why the number of pediatric transplants was projected to be stable. Dr. Gajewski replied that there are a limited number of patients and relatively few indications for transplants. Dr. Kurtzberg thought that the indications for pediatric transplantation would increase, and the outcomes for hemoglobinopathy would be much better in younger children. Moreover, with the advent of newborn screening for metabolic diseases being implemented in more States, there is a higher chance that newborns would be transplanted for diseases that were previously considered fatal. Dr. Gajewski responded that it would probably be easier to develop the capacity in the pediatric workforce to meet those challenges. Dr. Kurtzberg noted that hospitalists had worked well in her hospital. Dr. Gajewski stated that, with adult patients, it had been difficult for hospitalists to integrate cancer with general medical issues.

Dr. Fred Appelbaum commented that the National Cancer Policy Forum, a subcommittee of the Institute of Medicine (IOM), met in November 2008 on the problem of the overall oncology workforce. As the population ages, there are more patients with cancer, yet the number of training slots for oncologists has remained constant. Moreover, with more intensive therapies, patients are coming for treatment more often and are living twice as long. The meeting also noted a significant decrease in the number of people being trained in the therapy technology sector. One suggestion that came out of that meeting was to increase training in other mid-level professions, where training times are much shorter. Dr. Appelbaum noted that the IOM would issue a report of that meeting. Dr. Gajewski noted that a cancer diagnosis often brings older patients into the system, at which point they also are diagnosed with life-threatening co-morbidities that must be addressed along with the cancer.

Dr. Lubin identified several challenges. First, as pediatric patients survive longer, there is a need to identify internists who can take over those patients as they grow older. Second, there is a shortage of trained technicians who can translate the findings of stem cell research into therapies. Third, reimbursement poses serious constraints for transplant programs. Finally, he noted that patients who do not have resources do not have access to transplant services; and he urged the Council to address this aspect of health disparities.

Dr. Richard Champlin emphasized that the marketplace alone cannot respond to the workforce shortage because of the complex training and legal issues. Central planning and a coordinated Government response are required for all elements of the health care system. In adult patients, transplants are typically utilized to treat leukemia, lymphoma, and myeloma, which are diseases of the elderly. The aging population magnifies the need for additional hospital resources to support those patients.

Dr. Karl Blume asked Dr. Gajewski what the Council could do to address this issue. Dr. Gajewski requested that the Council:

- Recommend additional resources for medical education.
- Identify mechanisms to increase involvement of senior physicians in the training of medical students and residents.
- Recommend increases in compensation.
- Advise ASBMT and NMDP to conduct a definitive workforce study.

Dr. Blume responded that once the work groups had completed their current tasks and the recommendations had been submitted, Dr. Gajewski would be invited to present an update so that the Council could determine whether to take up this issue.

BMT for Myelodysplastic Syndromes (MDS)

- *Claudio Anasetti, MD, ACBSCT Member*

Dr. Anasetti began by noting that the best evidence indicates that BMT is the only established curative therapy for myelodsypastic syndromes (MDS), and 80 percent of MDS patients are age 65 or older. The CMS has not made a national coverage determination for BMT in MDS. However, BMT is covered by CMS after MDS evolution to acute myeloid leukemia (AML), when transplantation is less effective. Dr. Anasetti stated that the purpose of his presentation was to encourage the Council to support a consultation with CMS to review the data on MDS treatment options and outcomes.

Dr. Anasetti presented epidemiological data showing that the incidence of MDS varies greatly by age. There are fewer than four cases per 100,000 under age 65; the incidence per 100,000 increases to 15 between the ages of 65 and 75, and is greater than 30 for ages 75 and above. He noted that the median age of diagnosis is actually between 75 and 80.

Dr. Anasetti compared the French-American-British (FAB) and World Health Organization (WHO) classifications of MDS. He noted that classification has become more specific over time. The FAB classification, based mostly on morphology, was helpful in identifying the taxonomy of the disease, but it was not adequate to describe the various syndromes and predict outcomes with any precision. The WHO classification divided the types of refractory anemia in the FAB classification into various subtypes. The FAB classification of refractory anemia with excess blasts (RAEB)-in-transformation has been redefined as AML.

About half of the patients diagnosed with MDS present a cytogenetic abnormality. The most common are 5, 7, and 8; 10 to 20 percent have more high-risk, complex abnormalities.

Dr. Anasetti stated that the International MDS Risk Analysis Workshop developed an International Prognostic Scoring System (IPSS) risk score in 1997. The prognostic variables included percentage of blasts, karyotype, and number of cytopenias at diagnosis. Risk scores were assigned in four categories: Low, Intermediate-1 (Int-1), Intermediate-2 (Int-2), and High. The IPSS has remained the gold standard for classification of risk and assignment of therapies. Dr. Anasetti noted that attempts have been made to augment the current IPSS scoring system to include data parameters, such as transfusion requirement, or to incorporate the WHO taxonomy; but most clinicians continue to base their decisions on the IPSS.

Dr. Anasetti presented data on survival and AML progression by IPSS MDS risk classification, which showed a correlation between survival rate and IPSS risk score. He then presented data showing that the overall life expectancy from diagnosis for untreated patients is only 3.5 years. It is much lower for older patients.

A 2000 study (Cheson, et al) proposed that the treatment goal for patients with MDS should be based on the underlying disease risk. For patients at Low or Int-1 risk, who have the longest life expectancy, the goal should be improvement in hematopoiesis. For patients at Int-2 or High risk, whose lives are immediately endangered by the disease, the treatment goal should be survival. Dr. Anasetti outlined the clinical endpoints and management considerations for each risk group.

Dr. Anasetti outlined treatment options for MDS, by risk level. Treatment modalities for Low/Int-1 MDS include hematopoietic growth factors, iron chelators, immune modulators, and immuno suppressive therapy (IST). Dr. Anasetti noted that IST does not appear to extend survival for patients above the age of 60. Treatment modalities for Int-2/High risk MDS include chromatin remodeling, with two agents approved by the FDA (5-Azacitidine, Decitabine); AML-type chemotherapy; and stem cell transplant (both autologous and allogeneic).

Dr. Anasetti presented data on the effectiveness of chromatin remodeling and chemotherapy for Int-2/High risk MDS. Clinical trials showed that both 5-Azacytidine and Decitabine prolonged survival, compared to supportive care. Azacytidine was associated with a greater difference in survival time. It is unknown whether this was due to research design or differences in the drugs themselves. The results of intensive AML-type chemotherapy have been discouraging, with a 5-year survival rate of only eight percent.

Dr. Anasetti then turned to a discussion of transplantation for MDS. In the U.S., autologous transplantation has not been widely utilized; and Dr. Anasetti was unaware of any randomized trials. A large trial conducted in Europe in 2006 found that allografts were nearly twice as effective as autografts in extending disease-free survival following induction chemotherapy. Dr. Anasetti then reviewed several studies that addressed the impact of transplant timing. A study that compared three strategies for stem cell transplant (SCT) (SCT at diagnosis; delayed transplant, and SCT upon progression) found that patients at Int-2/High risk had the greatest increase in life expectancy following immediate transplant, while patients at Low to Int-1 risk could benefit from delaying transplantation until progression to higher stage of MDS.

Dr. Anasetti noted that in considering transplantation for older adults, it is important to acknowledge that the number of patients with comorbities increases with age. At age 59, most patients have at least one comorbidity, and nearly half have more than three. Dr. Anasetti introduced a hematopoietic cell transplantation (HCT)-specific comorbidity index developed by Dr. Mohamed Sorror, and he presented data showing that the comorbidity index is predictive of transplant outcome.

Dr. Anasetti discussed outcome data on transplantation from related or unrelated donors after reduced intensity conditioning. The tables showed that mortality, relapse, and survival rates were similar across age groups for both AML and MDS. Dr. Anasetti noted that the 3-year

survival rate for transplant patients over 65 (approximately one-third) was dramatically higher than the survival rate in the Azacytidine and Decitabine trials.

Dr. Anasetti presented and discussed detailed treatment algorithms for Low/Int-1 risk MDS and Int-2/High risk MDS. These algorithms were recently developed and include both standard of care and transplant. For Low/Int-1 risk MDS, the algorithm recommends SCT for patients with diagnoses other than anemia whose condition progresses following chromatin remodeling or investigational therapy. For Int-2/High risk MDS, the algorithm recommends SCT for patients for whom there is an allogeneic donor and the risk profile is favorable.

Dr. Anasetti reviewed current CMS coverage for allogeneic transplantation. Medicare's current National Coverage Determination (NCD) on SCT includes leukemia, aplastic anemia, leukemia in remission, severe combined immunodeficiency disease, and Wiskott-Aldrich syndrome. Dr. Anasetti noted that these are only a small proportion of the conditions for which transplants are performed on a daily basis. The only condition for which allogeneic transplantation is specifically not covered is multiple myeloma. The current NCD does not include allogeneic transplantation for MDS. Local coverage decisions can be made when the NCD has not been updated for many years, but this has not occurred for MDS.

Dr. Anasetti emphasized the need for CMS coverage of SCT for MDS. The disease affects an older population; there is evidence of clinical benefits of allogeneic transplant; and age, by itself, is not a limiting factor. The ASBMT and NMDP have supported an in-depth analysis of this issue and analysis of the available data. Both groups believe that investigation of NCD for allogeneic transplant for MDS is warranted. They are planning to consult with CMS regarding the best approach for conducting a review, and they will seek an informal meeting in early 2009.

Dr. Anasetti proposed that the Council endorse the effort by ASBMT and NMDP to pursue NCD for allogeneic transplant of MDS, in consultation with CMS.

Discussion

Dr. Champlin noted that AML and MDS are a continuum, with similar prognoses. Medicare requires patients to wait for a transplant until the percentage of blasts increases, when the outcome is clearly worse. He supported the effort to take this issue to CMS.

Dr. Blume asked whether additional work was needed before the Council could make an endorsement. Dr. Anasetti replied that it would be many years before additional data would be available. He clarified that he was not asking the Council to support national coverage. His request was for the Council to support the request for CMS to review the existing data. He hoped that the Council's endorsement could be secured before the informal meeting. The ASBMT Committee chairs would pursue strategies, according to the CMS recommendation.

Responding to a question from Dr. Charles Sims, Dr. Blume stated that this issue was within the scope of the Council's charge. He noted that the Council was not limited to addressing issues that were identified at previous meetings and was free to consider urgent issues as they arose.

He noted that this request was based on a significant amount of data gathered by the scientific community.

Dr. Appelbaum shared Dr. Sims' concern about the Council spreading itself too thin, but it should support this request because the lack of coverage for MDS transplantation had been a problem for many years.

Dr. Gajewski described his experience going before the CMS to address the issues of coverage for MDS and non-Hodgkin's lymphoma. A recommendation from the Council would be helpful.

Mr. Aronoff stated that the Council could vote now, but that first specific wording for a recommendation should be developed.

Dr. Champlin moved that the Council support the recommendation proposed by Dr. Anasetti. Dr. Kurtzberg seconded the motion.

Dr. Liana Harvath stated that the abstracts of the studies cited by Dr. Anasetti would be good supporting information and asked when they would be published. Dr. Anasetti replied that the abstract was published on November 15, 2008.

Dr. Blume asked whether the handout on National Comprehensive Cancer Network (NCCN) guidelines reflected the intent of Dr. Anasetti's request. Dr. Anasetti replied that the NCCN guidelines and the ASBMT position statement both recommended transplant for patients with IPSS score of 1.5 or greater (e.g., Int-2 or High), and other candidates whose features are not yet included in the IPSS but are expected to have poor prognosis. He noted that the ASBMT position statement had been distributed to Council members. The evidenced-based review was currently in press with Biology of Blood and Marrow Transplantation (BBMT) and would soon be available online.

Dr. Dennis Confer of the NMDP stated that ASBMT and NMDP would greatly appreciate the support of the Council. He asked whether the Council could strengthen its statement by encouraging the Division of Transplantation and HRSA to facilitate these activities. Dr. Appelbaum noted that the Council's recommendation would be submitted to the Secretary.

Dr. Blume requested that Dr. Anasetti develop a more detailed statement before the Council voted on the motion. The vote was scheduled for the end of the day.

Reports from Workgroups

Dr. Blume noted that the Council had met in January and April 2008 in Rockville, Maryland, and also had conducted numerous conference calls. The Council formed five work groups comprised of Council members and HRSA staff to address specific issues.

Cord Blood Bank Accreditation Organization and Recognition Process

Work Group Presentation and Council Discussion

- *E. J. Read, MD, Work Group Chair*

Mr. Aronoff noted that five Advisory Council members also served on the Board of Directors of the accrediting organizations. The Division consulted with the HRSA Ethics Advisor, who stated that those five members can participate in discussions of specifications for accreditation; they can vote on the specifications; and they can participate in discussions related to selection of one or more accrediting organizations. When there is a motion on the floor to vote on the selection of one or more accrediting organizations, those five members must recuse themselves and leave the room.

Dr. Read acknowledged the Advisory Council members and HRSA staff who participated in the work group. She noted that the recognition of one or more accreditation entities for the accreditation of cord blood banks was a requirement of the Stem Cell Therapeutic & Research Act (PL 109-129). The law also specified that the NCBI banks were to be accredited by the recognized organization(s). Prior to the formation of the Council, HRSA gave interim recognition to the AABB (formerly the American Association of Blood Banks) and FACT for the initial NCBI competitions. The interim decision was to be followed by a recognition process that allowed for input by the Advisory Council and the public.

At the ACBSCT's first meeting in January 2008, HRSA charged the Council with formulating and executing a plan for developing recommendations to the Secretary and HRSA regarding accreditation. The plan was to include a recommended recognition process, criteria for recognition, and the expertise and backgrounds of individuals to be involved in HRSA's recognition decision. The process of executing the plan would entail information gathering, including presentations by accrediting organizations, and development of proposed recommendations for Council deliberation.

The Accreditation Work Group was formed at the January meeting. Between January and April 2008, the work group reviewed and edited HRSA's Draft Specifications for Accreditation Organizations, drafted key questions for organizations to address during presentations at the April Council meeting, and invited AABB and FACT to present at that meeting. At the April 2008 meeting, the Council reviewed the Draft Specifications, heard informal presentations by AABB and FACT, and discussed the topic. From April through December, the work group refined the Draft Specifications, conducted a preliminary evaluation of AABB and FACT's ability to meet the Draft Specifications, compared AABB and FACT Standards, and discussed the process for accreditation recognition.

Dr. Read presented the work group's conclusions as of December 2008:

- The Draft Specifications are almost ready to be finalized.
- Based on the presentations by AABB and FACT at the April meeting, both organizations appeared to meet the Draft Specifications. A major generic item of concern for all cord blood banks (CBB) and inspections is the capture and analysis of post-distribution data (post-thaw quality control and outcomes), which is usually out of the CBB's control.
- A detailed comparison of AABB and FACT Standards identified no incompatibilities in requirements; differences appear to be in format, style, and level of detail. Additional

detail could be provided in HRSA-specific requirements and/or in future revisions to the organizations' standards.

Dr. Read stated that the work group's recommendations regarding the recognition decision should be reviewed by, and the final recommendation should come from, the entire Council. The work group proposed the following steps for recognition:

- Finalize the Draft Accreditation Specifications.
- HRSA to send formal letters asking AABB and FACT if they are able and willing to meet those specifications.
- Prior to the next Council meeting, the work group is to review AABB and FACT responses and formulate recommendations for recognition.
- At the next Council meeting, the Council is to vote on recommendations for recognition.

Dr. Blume thanked Dr. Read for her presentation and for her leadership of the work group.

Discussion

Dr. Robert Hartzman asked whether the inspection process would be focused on the Specifications and expressed concern that the process could become expensive or burdensome if inspectors were allowed to include items that were not included in the Specifications. Dr. Read replied that AABB and FACT have different methodologies and approaches to conducting inspections. The work group did not intend to add details to the Draft Specifications, but it would not want the accrediting organizations to do less than what the Specifications set forth. She noted that HRSA would be responsible for oversight and administration of the accreditation process.

Dr. Sims stated that accreditation agencies and inspectors have their own standards and criteria, which may go beyond those specified by HRSA. The work group felt that both organizations met the standards of the Draft Specifications. In the long run, the purpose of an inspection is to ensure the safety and effectiveness of the transplant. The inspection criteria must be flexible because the field of transplantation is not static.

Dr. Pablo Rubinstein stated that the there is no substitute for having inspections conducted by a well trained expert who understands the requirements. The accrediting organizations should not be discouraged from being as thorough as possible. Reducing the intensity of that process would be contrary to the rationale for conducting inspections.

Dr. Edgar Milford raised two issues. One is the accreditation of AABB and FACT, as independent organizations. The other is having AABB and FACT "deemed status" organizations for the Federal contract. He asked how many items beyond those currently required for their own accreditation process would need to be added to meet the requirements of the contract, such as data processing and reporting. Dr. Read replied that there were very few items, and they were more at the level of detail. For example, FACT has fairly detailed data collection requirements regarding times to engraftment; AABB does not specify that. Dr. Read noted that some of the contractual requirements for NCBI banks went beyond the standards for AABB and FACT and even the FDA's BLA standards. Dr. Milford asked if cord blood banks (CBB) would state up

front that they were applying for accreditation. Dr. Read stated that the Request for Proposal stipulates that CBB applying for NCBI funding must be accredited by one or both organizations.

Dr. Blume asked Dr. Read how long it would take to finalize the Draft Specifications. Dr. Read stated that the work group could finalize the document by the end of the meeting. Dr. Blume clarified that once the Draft Specifications were finalized, they would be sent to AABB and FACT to confirm that they could meet the specifications. AABB and FACT would submit their responses prior to the next meeting, and the Council would vote on a recommendation regarding recognition at the May meeting. The Council was scheduled to vote on the Draft Specifications on Tuesday morning.

Program Confidentiality Policies for Cord Blood Donors

Work Group Presentation and Council Discussion

- *Michelle Bishop, PhD, Work Group Chair*

Dr. Bishop acknowledged the work group members and HRSA staff who worked on this issue. She thanked Dr. Blume for participating in the conference calls, and acknowledged the feedback provided by Kathy Welte of the NMDP.

Dr. Bishop noted that confidentiality is critical to avoid unwelcome publicity, coercion, and adverse impact on other patient searches or donation, and to retain trust with donors and recipients. She reminded the Council that P.L.109-129 specifies information that cannot be disclosed for adult bone marrow donors, but it does not provide detail regarding confidentiality for cord blood donors. The work group was therefore charged with developing specific recommendations to address that gap.

At the Council meeting in April, the work group presented drafts of two main sets of recommendations. The first set addressed the disclosure of information to cord blood recipients and donors; the other set addressed the linkage between the cord blood donor and the donated unit. The work group also presented an additional recommendation stating that donation terminated the donor's ability to direct the use of cells, and another stating that these recommendations should apply to both private and public banks. The Council discussed these drafts in detail and suggested a number of revisions. Following the April meeting, the work group made several rounds of revisions to incorporate feedback from the Council and NMDP. The revised recommendations were included in the packet for this meeting.

Dr. Bishop presented a table showing how the work group had categorized each type of information as of the April meeting. Disclosure categories included: "Routinely Disclosed to Recipient," "Not Routinely Disclosed to Recipient," "Never Disclosed to Recipient," and "Never Disclosed to Donor." At the time of that meeting, the work group had not determined how to treat the name of the bank where the unit is stored and the code identifying the bank. During that meeting, Council members suggested those items should be moved from "Never Disclosed" to "Not Routinely Disclosed," along with the collection date, the collection month, and the status of the donated unit.

Following the April meeting, the work group discussed the proposed changes and noted that some were more problematic than others. The work group elected to divide the category of "Not Routinely Disclosed to Recipient" into "Not to be Routinely Disclosed to Recipient" and "Strongly Advised against Disclosure to Recipient (or Donor)." NMDP feedback indicated that the distinction between these categories was confusing; the work group ultimately chose to eliminate that distinction. Dr. Blume raised a concern about whether allele-level typing should be routinely disclosed. Based on NMDP feedback, the work group added this to the list of items that should be routinely disclosed.

Dr. Bishop presented a table showing the work group's current recommendations for disclosure of each type of information. The revised table included three categories: "Should Be Routinely Disclosed to Recipient," "Advised Against Disclosure to Recipient (or Donor)," and "Must Never be Disclosed to Recipient (or donor)." Information that the work group recommended for routine disclosure included the year the CBU was collected; donor sex; ABO/Rh; TNC of the unit; HLA of the unit; abnormal findings that may make the unit "ineligible" by FDA standards, though still clinically useable; abnormal findings that include risk regarding maternal health history; and abnormal findings that include hemoglobinopathies. Information that the work group advised against disclosing included whether the unit was foreign or domestic; name and code of the CBB where the unit is stored; collection date and month; and status of the donated unit. The only items that must never be disclosed were donor race, donor name or contact information, and recipient name or contact information.

Dr. Bishop then reviewed linkage issues. In April, the work group recommended linkages between the donor and the CBB so the bank could inform the donor mother of abnormalities, and the donor mother could inform the bank of the child's health. The work group recommended that there be no limits on the number of contacts, and that records should be retained until the CBU was used or discarded. Subsequent to that meeting, the work group strengthened these provisions because linkages between donor and bank are required by regulatory agencies and are considered part of good tissue practices. It also revised the recommendations to state that CBU records be retained for a minimum of 10 years after the cord is used or discarded, to be consistent with the AABB standard. The work group also clarified the language of the document in several other areas.

Dr. Bishop discussed the status of several additional issues. The issue of whether the recommendations should apply to private as well as public banks has been dropped, at the advice of the Council. The work group discussed several other questions, including limits of rights, whether donor mothers can rescind consent or redirect use of the unit, whether donor mothers can consent only to clinical use, and whether the consent form needs to mention future research. The work group concluded that these were issues of consent, and not confidentiality.

Discussion

Dr. Milford suggested that clinicians and CBBs would most likely want to know what information they must disclose and must never disclose, and what types of information could be disclosed at their discretion. He asked Dr. Bishop to clarify the meaning of "Should be Routinely Disclosed." Dr. Bishop stated that disclosure of the items in that category should be

standard practice, while allowing some discretion. Dr. Blume noted that IRBs strongly recommend communicating with patients at a sixth-grade level. He was concerned that consent forms and counseling sessions include complex medical terms, and it is not in the patient's best interest to be presented with information that they cannot understand. It is essential for the recommendations to include room for clinical judgment so that they are appropriate for patients and the transplant community.

Dr. Champlin stated that the most important area of confidentiality was the types of information that must never be disclosed. He felt that information that did not need to remain secret should not be withheld from patients.

Dr. Kurtzberg stated that medically important information, such as sex and blood type, must be disclosed to avoid medical errors and to enable patients to transmit that information to other providers at a later date. She felt that as much information as possible should be left to professional discretion because families that want to know can obtain information in other ways. She expressed concern about including donor race in the category of "Must Never be Disclosed."

Dr. Sims stated that the critical issue is what goes in the medical chart. The Council needs to be careful about stipulating information that cannot go into a chart. He also noted that the Council had not addressed the issue of informed consent and recommended forming a work group to study that issue.

Dr. Appelbaum noted that all of the items in the second column ("Advised Against Disclosure to Recipient (or Donor)") are in the medical chart or the working records of the unrelated donor programs and are therefore discoverable. In some institutions, patients can access their record on a daily basis. Other records, such as lab records, are not part of the medical record; these are discoverable, but not easily accessible. He felt that the work group had done a good job of classifying the information. He cautioned that making the guidelines too strict could put hospitals at risk of non-compliance with laws regarding patient rights.

Dr. Hartzman expressed concern that disclosure of the collection date could make it possible to identify the donor. Dr. Kurtzberg noted that this information is in the paperwork that accompanies the unit and is in the medical chart. Another Council member added that multiple identifiers help to ensure that the patient receives the right unit.

Ms. Susan Stewart agreed that information should be communicated to patients at a level they can understand, but information at all levels should be made available to patients at their request.

Mr. Stephen Sprague noted that all of the items in first two columns were at the discretion of the physician. Dr. Blume stated that the title of the column would determine the level at which it would be enforced.

Dr. Lubin suggested replacing "hemoglobinopathies" with "hemoglobin traits." He asked whether the recommendations addressed double-cord procedures. Dr. Champlin stated that the confidentiality issues would be the same; a double-cord procedure would use a separate form for

each cord. He noted that donor race is included in the documentation that accompanies each bag and is therefore discoverable. He recommended moving it to the middle column.

Dr. Robyn Yim expressed concern that information on the location of collection should not be disclosed. This information provides a link between the donor and the unit, especially for small banks that may only collect one unit per week. Dr. Champlin acknowledged her concern, but he noted that this information is on the bag.

Dr. Read was concerned about disclosing donor birth date. She recommended using other identifiers, such as a sequential number from the bank. A representative of the ISBT noted that the unique unit identifier includes an alphabetic symbol for the country of origin, plus the year the unit was manufactured. It does not include a month. Dr. Read stated that this would be a solution going forward, but it would not affect units that were already banked. Dr. Sims noted that units are shipped around the world. He cautioned against relabeling bags or prescribing labeling.

Noting that linkage would now be required, Dr. Matthew Kuehnert asked what would happen if a mother refused. Dr. Bishop replied that she would not be allowed to donate the cord.

Dr. Blume asked what the next steps would be. Dr. Bishop replied that some of the proposed changes were clear, such as moving donor race to "Advised Against Disclosure" and changing "hemoglobinopathies" to "hemoglobin traits." Beyond that, the work group would need to know whether the Council was comfortable with the language in the draft recommendations included in the packet for the meeting. Dr. Pentz noted that the Council's comments were contradictory; the work group would need specific feedback.

Council members engaged in further discussion regarding the wording of the column headings. Numerous suggestions were made regarding the wording of the column headings. There was general agreement that information affecting the outcome of a transplant must be disclosed, that the language should leave room for the professional judgment of the health care team, and that it was essential to protect the privacy and confidentiality of cord blood donors.

Dr. Ellen Lazarus requested that Council members contact her by email if they had specific recommendations regarding labeling requirements.

Dr. Blume asked the work group to reconvene and discuss the wording of the column headings and develop wording for the recommendation.

Need for Public Funding for Required Data Documentation

Work Group Presentation and Council Discussion

- *Doug Rizzo, MD, MS, SCTOD Project Director, Associate Scientific Director, CIBMTR Milwaukee Campus*

Dr. Rizzo presented on behalf of the work group that was formed to address the potential need for public funding for required data documentation. As background information, Dr. Rizzo

presented the findings of two studies conducted by CIBMTR to better understand the data collection burden.

Dr. Rizzo noted that there had been a change in scope of data for the HRSA program. Prior to 2005, the requirement was to collect data on all unrelated hematopoietic stem cell transplants (HSCT) facilitated by the National Bone Marrow Donor Registry. Data was collected on the Comprehensive Report Forms. The Stem Cell Act of 2005 included a requirement to collect data on all allogeneic (e.g., related and unrelated) HSCTs. A more limited data collection instrument was developed for that purpose.

Dr. Rizzo outlined the extensive scope of the required data collection, analysis, and dissemination under the new program. He emphasized that CIBMTR has made efforts to make the data collection process as reasonable as possible, but a significant amount of information is needed to meet the objectives of the program. Data collection instruments include: Unique ID Form, which enables SCTOD to link cord blood bank data to recipient outcome data; Pre-Transplant Essential Data (TED) and Post-TED Forms that provide information on the transplant itself; Death Form; HLA Form to collect data on HLA typing; Infectious Disease Markers Form; and Infusion Form. Dr. Rizzo noted that the Infusion Form was developed to understand what happens to a unit before and after transfusion and any adverse events that may occur. All of the forms were approved by the Office of Management and Budget in October 2007.

Dr. Rizzo presented preliminary results of a survey that CIBMTR conducted to understand the burden of the required data collection. He noted that detailed responses to each question were included in the packet for the meeting. Survey questions obtained data on center characteristics, level of participation in CIBMTR, data collection resources, responsibilities of data staff, and time studies (e.g., time required to collect data, complete paper or electronic forms, and total time). CIBMTR sent the survey to approximately 500 primary contacts around the world; 120 centers responded. Dr. Rizzo outlined the demographics of the centers that participated in the survey. He noted that most respondents were U.S.-based centers that performed adult HSCT; about half performed pediatric transplants. Ninety percent had their own database, but only about one-third had dedicated information technology staff. Nearly half of the databases were Excel or Access-based. Among centers with their own database, only 19 percent imported data from electronic health records.

The survey found that, in general, centers with less than 100 HSCT per year had 1 full-time equivalent (FTE) staff member assigned to data-related activities. Fewer than 30 percent of the centers had dedicated staff to collect long-term follow-up data. Data collection staff had a wide range of responsibilities, aside from providing data to CIBMTR.

Dr. Rizzo noted that not all respondents participated in the time survey; there were only 60-80 responses per question. The high-end outliers across all questions were dominated by 4-5 responses. The inter-quartile range (25th-75th percentiles) was tight around the median. The median times to complete the electronic (FormsNet) and paper version of each form were:

- Unique ID: 21 minutes (FormsNet); 28 minutes (paper)
- Pre-TED: 85 minutes (both formats)
- Post-TED: 75 minutes (FormsNet); 80 minutes (paper)

- Infectious Disease Markers: 43 minutes (FormsNet); 50 minutes (paper)
- HLA Typing: 35 minutes (FormsNet); 40 minutes (paper)
- Infusion Form: 73 minutes (both formats)
- Death Form: 40 minutes (FormsNet); 45 minutes (paper)

The next steps for CIBMTR will be to review the data for patterns by center characteristics and conduct a multivariate analysis to determine whether center-related factors are associated with particularly long or short times to complete the required data collection. CIBMTR will provide the survey results to data staff and leadership at the centers that responded to assist them in identifying ways to streamline their data collection process. Dr. Rizzo noted that this survey identified early frustration with the FormsNet system and the mandatory data reporting requirements. He suggested that it would be useful to conduct a follow-up survey once centers have had time to become familiar with the forms and the systems.

Dr. Rizzo turned to a discussion of the potential of AGNIS (A Growable Network Information System) to support data collection for this program. He noted that AGNIS was designed to be a public electronic system to facilitate data sharing between transplant programs, although its data can be shared between any two nodes on a public system. AGNIS was developed through a grant from the National Cancer Institute (NCI), and it is not proprietary. It is an open-source messaging system with appropriate security and audit trails. It incorporates standard data elements, as defined in the NCI cancer Data Standards Repository (caDSR). Dr. Rizzo noted that AGNIS could help this program by leveraging existing electronic database systems at centers to reduce reliance on human data staff in favor of scalable, programmable systems. AGNIS also facilitates data exchange across participating networks, which promotes collaborative research.

Dr. Rizzo cautioned that AGNIS is not a panacea and implementing AGNIS is hard work. CIBMTR currently has three beta test sites, all of which are reasonably large centers with dedicated IT resources. Challenges include mapping data from the user's electronic systems to the data standard. Dr. Rizzo described three case scenarios for AGNIS: integrated AGNIS, in which the center's database is mapped and connected to CIBMTR to provide synchronized data for all patients; third-party applications, in which AGNIS is used to deliver FormsNet data to the center; and AGNIS alone, in which AGNIS is used to retrieve FormsNet data and populate a local database.

To illustrate the resources required for data mapping, Dr. Rizzo presented a table showing the number of data elements for each SCTOD form, the estimated number of days it would take to map those elements and conduct quality assurance, and the estimated FTE required to perform those tasks. The resources needed include approximately 0.6 FTE for development and testing of the SCTOD forms; an experienced content expert at 0.2-0.2 FTE; a database administrator at 0.2-0.3 FTE per FTE developer; and a systems administrator at 0.1 FTE. Server costs are less than $5,000. Dr. Rizzo noted that these estimates were based on the three beta sites.

The next steps for AGNIS include completing all data elements for the SCTOD forms in the caDSR system and programming for data sharing and exchange. Both steps are scheduled for

completion in January 2009. Dr. Rizzo stated that greater expertise and experience in mapping would provide lessons learned for later adopters, as well as better time and resource estimates.

Discussion

Responding to a question from the Council, Dr. Rizzo confirmed that mapping is usually a one-time effort. He noted that the mapping would need to be changed to reflect revisions to an electronic health record or an SCTOD form. At this point in time, it is difficult to estimate the level of effort that would it require. Dr. Rizzo noted that CIBMTR would publish any changes to SCTOD forms, which would help with mapping.

Dr. Appelbaum acknowledged that the data collection process was complicated, and it was not likely to improve soon. There is no uniform electronic medical record (EMR) system. Each center is unique. He noted that the time estimates for mapping the SCTOD forms were not an exaggeration. AGNIS requires a significant investment, and it may not make sense for smaller centers. Dr. Rizzo noted that future iterations of EMR systems may become more standardized. It may not be time for smaller centers to invest in AGNIS; however, a fair amount of the data collected for the SCTOD could be used for their own quality assurance purposes.

A member of the public agreed that data collection requires time, effort, and money. It is easy to legislate data collection without understanding the implications on day-to-day work. We have the opportunity to build systems that will provide small-to-medium size centers with access to their data and improved reporting capabilities. Centers that will benefit from AGNIS are those with systems that already do everything they want. There is no way to get around the fact that someone has to enter the data. The issue for the Council is who will be asked to make that investment.

Dr. Blume noted that this topic was included in the agenda because transplant centers are expected to provide the data, and centers want to know who will cover the cost of data collection. The centers expect the Council to make a recommendation.

Dr. Champlin stated that bigger centers are more likely to get institutional support. The quality of the data will suffer without sufficient funding. It is irresponsible to treat data collection as an unfunded mandate. The cost for data collection should be included in funding for the program. Another option would be to include it in the cost of a transplant, similar to a mechanism used by the NMDP for bone marrow transplants.

Dr. Appelbaum asked for an estimate of the true FTE cost of data collection per transplant, including median hours for all data forms, per patient. Dr. Rizzo stated that CIBMTR could prepare those scenarios. Dr. Blume said that would be helpful.

Dr. Kurtzberg asked if the Council could discuss a request for funding to support data collection. Dr. Appelbaum suggested that the Council express its concern about unfunded mandates. Dr. Blume noted that hospitals did not face any consequences for failing to provide the required data. Dr. Rizzo expressed concerns about threatening hospitals with penalties. He thought that incentives would be more productive.

Dr. Milford stated that he was involved in the solid organ transplant program. Administrators recognize that data collection is an essential part of a viable transplant program, and they usually provide the resources. It is important to make centers aware of the data collection requirements and the consequences of non-compliance. Dr. Rizzo outlined the steps that CIBMTR was taking to increase awareness of the data collection requirements.

Dr. Appelbaum noted that hospitals are non-profit. If funding is not provided for additional data collection requirements, hospitals have to cut other programs. Someone must pay for the services, whether it is patients or the Federal Government.

Mr. Baitty stated that the SCTOD contract precludes CIBMTR from using HRSA funds to reimburse transplant centers for data submission. He said this decision was made in view of the solid organ community's successful incorporation of mandatory data reporting as a cost of doing business in their pricing to insurers, and because paying for data submission from appropriations for the Program at its current levels would come at the cost of reductions in the parts of the Program that help patients obtain transplants such as recruitment and tissue typing of adult donors and direct services to patients.

Dr. Mary Horowitz of CIBMTR estimated that a realistic number would be 1-1.5 FTEs per 100 patients. She emphasized the importance of developing a document that could be provided to administrators. Dr. Blume clarified that the Council could submit a recommendation to the Secretary.

Dr. James Bowman reported that a significant amount of funding had been allocated to health information technology (HIT). He suggested that the Council recommend that the Secretary consider using discretionary HIT funding for this purpose. The group also discussed the option for individual Council members to contact their congressional representatives as private citizens to advocate for additional funding next year.

Dr. Rizzo thought that Dr. Bowman's suggestion might dovetail with work on AGNIS. He noted that the NCI had devoted approximately three FTEs to AGNIS, including efforts related to this aspect of the project. There has been some interest in having NCI look at implementation projects surrounding AGNIS, and granting agencies may be interested in funding implementation projects that bring organizations to data standards.

Dr. Milford stated that data collection is an essential aspect of the Program. He expressed support for Dr. Champlin's suggestion of increasing the cost of products or services to compensate for data collection, and he asked whether it was feasible to develop a common data collection system for use across transplant systems.

Dr. Anasetti stated that labor was required to enter data, regardless of the software system. Eventually data entry will be done once, but labor will still be required to extract and interpret the data. Dr. Rizzo noted that some variables are direct, while others are transformed. He asked whether there might be ways to leverage data collection in the clinic environment so that there is a closer relationship between the data collected and the data provided.

Dr. Rubinstein stated that the mandated data collection has had a negative impact on the ability of his center to collect data directly from the transplant center. He noted that his center's data collection had decreased from an average of 92 percent to less than 50 percent in less than one year. He expressed concern about the ability to effectively monitor the results of his center's grafts. Until such time that a centralized system can provide the data in a timely manner, centers are losing information that has long been important to maintaining quality. In the meantime, transplant centers should be asked to continue to provide the abbreviated information as they had in the past. Dr. Kurtzberg noted that the New York Blood Center has a unique mechanism for data collection. The intent of the SCTOD was to centralize the receipt and release of data. The challenge is to find a way to get data from the cord blood program more quickly.

Dr. Appelbaum stated that while the cost of data collection is relatively small, it is still an unreimbursed expense. Noting that the Council did not want to divert funds from other aspects of the Program, he asked whether any discretionary funds were available. Mr. Aronoff replied that the Division of Transplantation and HRSA do not have funds that could be reallocated to data collection; and he was skeptical about the prospects of asking the Secretary to provide additional funds.

Dr. Kurtzberg stated that hospitals make decisions about how to use funds. They are not likely to allocate funds for data collection unless they are mandated to do so.

Dr. Blume asked what the next steps would be. Dr. Appelbaum suggested that the Council recommend that the Secretary seek additional funding to support 1.5 FTE per 100 transplants for data collection, since this is a mandated activity. Dr. Blume agreed that the CIBMTR survey provided sufficient data to support a recommendation. He asked Dr. Appelbaum's work group to develop a recommendation regarding funding to cover the incremental cost of mandated reporting for SCTOD forms.

Dr. Jeff Chell of the NMDP stated that the estimated cost to cover the required reporting would be about $1,000 per transplant, for a total of about $10 million. He suggested that the Council recommend an increased appropriation as part of the reauthorization process.

Mr. Durbin noted that, in addition to the Government, the primary beneficiaries of data collection are the patients and insurers. The solid organ transplantation program found that insurers assume that they are paying for the cost of data collection. Dr. Horowitz noted that many insurers require transplant centers to provide outcome data in addition to what they must provide to the SCTOD.

Dr. Appelbaum clarified that additional funding was not being requested for data collection. Centers have been collecting data for many years. The requested funding is for the incremental cost to report the data in a different format, using different forms.

Dr. Rizzo stated that most centers indicated it took more time to collect the data than to provide it to CIBMTR. Reporting the data may take slightly more than half of the time reported in the survey. Dr. Horowitz stated that her estimate of 1.5 FTE included the costs of collecting data for

all purposes. She stated that the incremental costs would be somewhat less than 1.5 FTE for centers that have a well-developed data collection system, but it would probably not be less than 1.0 FTE per 100 patients.

Dr. Appelbaum agreed that the work group would draft a recommendation to the Secretary to request funding to cover the additional cost of completing SCTOD forms, while acknowledging that a certain portion of the data collection costs were specific to each center.

Dr. Blume noted that there would be three additional presentations following the break. Dr. Anasetti would present the draft motion regarding MDS; Dr. Bishop would present the most recent version of the confidentiality table; and Dr. Kurtzberg would make a presentation on the FDA issue that was discussed by conference call.

Draft Motion Regarding MDS

- *Claudio Anasetti, MD, ACBSCT Member*

Dr. Anasetti presented the text for a Council recommendation related to MDS:

- MDS and AML are life-threatening blood disorders that are often part of the same disease process continuum.
- There is strong evidence for the benefit of allo-SCT in the treatment of AML.
- There is strong evidence for the benefit of allo-SCT for MDS in patients less than 65 years, and growing evidence in patients greater than 65 years.
- There is also evidence that comorbidities may have a greater impact than age on allo-SCT outcomes in older adults.

Based on these findings, the ACBSCT recommends consideration of the use of allo-SCT for MDS and recommends that the Secretary instruct CMS, as a high priority, to develop an appropriate strategy for NCD.

A motion to approve the recommendation as presented by Dr. Anasetti was made and seconded, and it was passed unanimously by voting members.

Revised Confidentiality Table

- *Michelle Bishop, PhD, Work Group Chair*

Dr. Bishop presented the work group's proposed modifications to the confidentiality table, which were then edited further by the Council. She noted that, as suggested earlier, donor race had been moved from "Must Never Be Disclosed" to "Advised Against Disclosure."

The Council discussed the appropriate term to replace "hemoglobinopathies" and agreed upon the term "genetic hemoglobin abnormalities."

Dr. Bishop noted that the work group added an asterisk to the first column heading to reflect the Council's concern about flexibility for professional discretion. With the footnote, the column heading would read, "Should be Routinely Disclosed to Recipient*" "*in a clinically appropriate

manner, or in greater detail upon patient request." The Council agreed that the modified wording was acceptable and did not suggest any further changes.

The Council discussed the wording of the second column, "Advised Against Disclosure to Recipient (or Donor)." Some Council members thought the wording was too strong; others thought it was not strong enough. After discussion, the heading was modified to "Not Recommended for Routine Disclosure to Recipient (or Donor)." The word "routinely" was subsequently removed to strengthen the statement. The final version stated: "Not Recommended for Disclosure to Recipient (or Donor)."

Dr. Bishop noted that the work group added a footnote to three items in the second column (name of CB bank, collection date, and collection month). The footnote read: "It is recommended that this information be considered to be withheld from labeling and medical records do not require its inclusion." This statement recognized that the labeling and records for cords that had already been collected could not be changed, while recommending changes for future labeling.

Dr. Harvath stated that the FDA's final rule for these products specify the information that must be on the label. The FDA's definition of labeling for blood products includes records that accompany the unit when it is shipped for transplant. Dr. Lazarus asked the Council to provide a list of items that were in contention so that she could check them against the FDA requirements. Dr. Sims noted that the Council has no direct control over labeling. He suggested that the issue of labeling be dropped for the time being, since it could not be resolved. Dr. Bishop removed the footnote from the revised table.

Dr. Appelbaum asked if the proposed changes would raise any concerns for donor consent. Dr. Yim replied that the revisions would change the nature of informed consent. Donors would need to be told that information in the first two categories could potentially be shared. Council members noted that this information is on the labels of thousands of units that are already in storage. Dr. Appelbaum stated that the proposed classification of each type of information reflected current reality. Dr. Yim suggested that information be encrypted at the collection site. Dr. Read stated that the key issue was informed consent. Dr. Appelbaum noted that the consent form would have to indicate that the items in the second column could potentially be disclosed to the recipient. The question was whether the small risk of disclosure would discourage potential donors.

A motion to accept the revised table was made and seconded, and it was passed unanimously by voting members. The approved table is attached to these minutes.

FDA/HRSA Conference Call Re: Potency Guidance

- *Joanne Kurtzberg, MD*

Dr. Kurtzberg reported on a conference call regarding potency guidance. She noted that the FDA recently issued guidance for measurement of potency of cellular and gene therapy products. HRSA arranged a conference call between Dr. Lazarus, Dr. Kurtzberg, Ms. Donna Regan, and

staff from the Division of Transplantation to address questions regarding the recently issued potency guidance and the draft guidance on cord blood licensure.

Dr. Kurtzberg stated that the potency guidance does not affect the draft guidance for cord blood licensure. ("Guidance for Industry. Minimally Manipulated, Unrelated, Allogeneic Placenta/Umbilical Cord Blood Intended for Hematopoietic Reconstitution in Patients with Hematological Malignancies. Draft Guidance.") The draft guidance states that potency for cord blood is defined on the pre-cryopreservation product.

Dr. Kurtzberg stated that the potency guidance does not address release criteria, which is a different topic. Dr. Lazarus stated that it is important to distinguish between selection criteria and recommended potency testing. For example, a cord blood manufacturer may use viable CD-34 cells and total nucleated cell (TNC) count as measures of product potency, whereas the transplant physician may select a cord blood unit (CBU) based on one of those measures and disregard the other. The fact that a potency assay is a recommended test does not limit the transplant physician's ability to use any available information to select a unit.

The conference call clarified that the responsibilities of the manufacturer of the CBU (e.g. the bank) end at the distribution of the unit. The manufacturer is not responsible for events that occur at the transplant center.

The manufacturer is responsible for providing materials that include the certificate of analysis (COA) and instructions for thawing and administration of the CBU to the transplant center with each cord blood product that is distributed.

At this time, Dr. Blume opened the floor for public comment.

Public Comment

There were no public comments.

Dr. Blume adjourned the meeting for the day at 4:30 p.m.

TUESDAY, DECEMBER 16, 2008

Dr. Blume called the meeting to order and asked Dr. Kurtzberg to present the report from the Work Group on Scientific Factors Necessary to Define a CBU as High Quality.

Scientific Factors Necessary to Define a CBU as High Quality

Work Group Presentation and Council Discussion

- *Joanne Kurtzberg, MD, Work Group Chair*

Dr. Kurtzberg presented the report on behalf of the work group that was tasked with scientific factors that identify a high quality CBU. She noted that the work group had previously talked about which parameters of banked CBUs predict engraftment and survival. At the moment, only cell dose and HLA have been shown to predict survival. Many researchers are attempting to develop and validate a more sensitive assay and have studied total nucleated cell (TNC), CD34, and Colony Forming Unit (CFU) in proficiency. Researchers are also attempting to determine which parameters of the graft correlate with potency.

Dr. Kurtzberg focused her presentation on a study she conducted to determine whether potency of a cord blood unit could be predicted from assays on frozen attached segments. She noted that the post-doctoral student who assisted her with the study was the first pediatric transplant patient at Duke.

Dr. Kurtzberg reviewed the guiding principles for evaluating the potency of CBUs. She noted that there are two decision points: pre-cryopreservation (precryo), and release for transplant. The pre-cryopreservation evaluation determines whether the unit is qualified for banking and licensure. It is based on TNC, CD34, CFU, HLA typing, maternal ID testing, and hemoglobinopathy screening. Dr. Kurtzberg noted that the FDA draft guidance defines potency requirements for CBUs based on a 20 kilogram recipient. The guidance requires at least 500 million TNC, at least 1.5 million viable CD34 cells, with a total viability of 85 percent. Dr. Kurtzberg stated that these are very reasonable guidelines for a pediatric patient, but they would not be sufficient for an adult. The NMDP and NCBI criteria stipulate 900 million cells, post processing. Dr. Kurtzberg stated that there are no specific guidelines at the point of release for transplant, aside from HLA confirmation. Some labs are looking at TNC/viability, CD34, or CFU. Other assays include HALO, viable CD34, and ALDHbright.

The clinical data currently support the fact that the precryo TNC and degree of HLA match predict engraftment and survival. Precryo CD34 has been predictive in some labs, but it has been difficult to standardize that assay. More recent research has shown that post-thaw CFU or post-thaw CD34 can also be predictive of engraftment, with or without a viability assay. Researchers are attempting to determine whether it is possible to take the precryo assessment of the CBU or a post-thaw assessment to develop an equation that would be more predictive of engraftment. Dr. Kurtzberg noted that other factors within the patient could affect the potency of the CBU. She also noted that some units that look good prior to freezing are not as potent when they are thawed.

Dr. Kurtzberg presented data from a study that she published a few months ago that looked at pre-cryo and post-thaw parameters and their ability to predict engraftment. The study included 150 children transplanted at her center for metabolic diseases, for whom the median cell count per dose was very high. The pre-cryo data came from various banks; post-thaw data were all collected at Duke. The data on overall survival by cell dose showed that post-thaw CD34 was a significant factor, while the post-thaw CFU was most predictive of survival. Dr. Kurtzberg noted that post-thaw CFU, which requires that cells give rise to colonies over two weeks, was the only functional assay in the study. The CD34 and TNC assays only indicate that a cell can be observed post-thaw.

Dr. Kurtzberg presented data comparing rates of neutrophil engraftment for pre-cryo and post-thaw CFU and CD34. Once again, pre- and post-thaw CFU had the best ability to predict platelet engraftment. The researchers also took patients from the same group who engrafted rapidly and patients who engrafted slowly and looked at the relationship between cryo-preserved CFU versus what was recovered post-thaw. They found that patients with higher pre- and post-thaw CFU had the best engraftment, while those with low pre- and post-thaw CFU had the worst outcomes.

Multivariate analysis for both survival and engraftment outcomes showed that post-thaw CFU was the most significant parameter. Post-thaw CD34 was also significant, but pre-and post-thaw TNC was not. Those findings were consistent for both engraftment and survival. Dr. Kurtzberg noted that performance status of the patient also had an impact, but the data were not graphed.

Based on that study, the researchers studied a group of 422 patients who had been transplanted with cord blood to determine whether pre-cryo, post-thaw, or a combination would be most predictive of neutrophil or platelet engraftment. The findings of this study echoed the themes of the previous study. A multivariate analysis found that pre-cryo CD34 best predicted neutrophil engraftment, but TNC best predicted platelet engraftment. Post-thaw CFU best predicted both neutrophil and platelet engraftment, although post-thaw CD34 was also predictive.

Dr. Kurtzberg presented data from a flow-based assay of segments from four CBUs that found a large degree of variability between cord blood units post thaw. These findings illustrate the difficulty of determining which unit should be selected for transplantation. If the transplantation is for a ten-kilogram child and the bank has ten times more cord blood than is needed, it is not a problem if only half of the cells are viable. It is a different issue if the patient is an adult.

Dr. Kurtzberg stated that the interim conclusion of these studies was that post-thaw CFU, measured from samples from the thawed CBU bag, best correlates with engraftment. The challenges of the CFU assay are that it is hard to standardize, and the assay is long (approximately 2 weeks), but the median time from a request for confirmatory typing of a unit and placement of an order for that unit is only 11 days. Possible solutions would be to develop a rapid assay that correlates with CFU contents, or develop a more rapid CFU assay.

Dr. Kurtzberg presented the hypotheses for the next study:

- CBUs, selected on the basis of pre-cryo TNC, may have sustained damage in the freeze/thaw procedures that reduce the potency of the unit at transplantation.

- Potency can be predicted on the basis of functional assays performed on a thawed segment attached to the banked CBU.

The experiment took assay segments from 40 CBUs stored at the time of unrelated CB transplantation for both rapid and non-engrafting patients. The objectives of the study were to determine which assay or combination of assays would be predictive, to determine the need, if any, for additional retrospective analyses, and to propose a prospective study based on the results of this study. Frozen segments retained and stored under liquid nitrogen after transplantation were thawed in Dextran Albumin and assayed. Samples were selected from a pool of patients undergoing myeloablative single cord transplantation who were either rapid engrafters or who failed to engraft. The researchers performed a variety of assays, including TNC, viability (TB), CFU, Halo, and five separate tests of flow cytometry. Dr. Kurtzberg presented data from the ALDHbright assay and described the characteristics of this type of test.

Dr. Kurtzberg presented data on the CD34, ALDHbright, and ALDHdim assays. The constant theme was that the numbers were always higher in the engrafter group than in non-engrafters, with the exception of ALDHdim. She then presented graphic representations of the data, which showed dramatic differences between the grafters and non-engrafters.

Interim conclusions from this preliminary study were that engraftment was predicted by (in ranked order): ALDHbright cells/kg, ALDHbright/CD34+ cells/kg, CD34/kg, and CFUs. Further data is needed to evaluate the HALO assay.

Dr. Kurtzberg presented data from a fresh CBU study that was conducted to find a shorter, more reliable assay that would best correlate with CFUs. In this study, 3,000 consecutively banked CBUs at the Duke CBB were assayed pre-cryopreservation for TNC, Viability (TB and 7AAD), CD34, CFU, ALDHbr, and GlyA. The researchers calculated that one CFU could be grown for every two CD34 cells, for every 1.2 ALDHbr cells, and for every one ALDHbr/CD34pos cell.

The interim conclusions of this study were as follows:

- In this small series, ALDHbr cell content of a thawed segment from a cryopreseved CBU can predict engraftment more than 90 percent of the time.
- ALDHbr content more accurately predicts engraftment compared to CFU, CD34, Viable CD34, or TNC measured on the segment.
- Correlations between segments and bags are needed in order to better understand the data.

Dr. Kurtzberg stated that the dilemma is that, per the FDA draft guidance, CBBs will gather data at the time of cryopreservation on TNC, viability, and CD34. CBBs will also continue to gather data on CFU and ALDHbr, and may conduct other assays. Before the CBU is released for transplantation, CBBs thaw the segment and test HLA for confirmatory typing. Various banks have other practices about testing for TNC viability, CD34, ADHbr, or other assays. It is currently unknown which of those assays will be predictive. If other assays are developed, those should be used as well.

Dr. Kurtzberg proposed the following studies:

- Continue with a limited center, retrospective study to compare segment versus bag content of TNC, CFU, CD34, HALO, ALDHbr cells to establish the relationship between values in the segment versus those in the bag.
- Conduct a multi-center, prospective study of 100 to 200 samples to determine which studies on thawed segments can predict engraftment (potency) of a banked CBU.

Dr. Kurtzberg recommended that these studies should be conducted by the banks, not the transplant centers, because they can get more meaningful data. She expressed the hope that HRSA could support this type of study through NMDP funds. A sub-study could look at double cords.

Discussion

Dr. Harold Broxmeyer asked why CD34 was ranked more highly in the final study, when CFU was a better predictor in the earlier studies. Dr. Kurtzberg replied that CFU was most predictive from samples obtained from the bags of the CBU, but it was not more predictive than CD34 in pre-cryo segments. The fresh CBU study also used a more rapid assay. Dr. Kurtzberg stated that the HALO assay is a 5-day assay. She is aiming for a same-day assay, but the feasibility is constrained by the logistics of segment.

Responding to Dr. Milford, Dr. Kurtzberg confirmed the she hoped that the ALDHbr, CD34 viable cell count in the segment might correlate with both CFU and potency and could be assayed immediately.

Dr. Kurtzberg told Dr. Blume that she envisioned that four centers would participate in the limited retrospective study. A multicenter study would involve eight or nine banks. Dr. Harvath stated that the proposed multicenter prospective study was exactly the type of work that NIH is looking for, and she encouraged Dr. Kurtzberg to submit a proposal to the National Heart Lung and Blood Institute (NHLBI).

Dr. Champlin raised a question regarding the ethics of withholding or transplanting a unit that testing indicated was non-viable. He urged that the proposed prospective studies include safety considerations for the patient.

Dr. Read suggested choosing the largest transplant centers that receive many units from different banks for the prospective study. Dr. Kurtzberg noted that Duke University is one of the largest transplant centers. She suggested that the research component of NMDP could determine which banks should participate.

Dr. Appelbaum asked how many transplant centers actually save segments. Dr. Kurtzberg stated that not many centers do that. Dr. Rubinstein stated that his blood center routinely saves segments, and he identified a number of issues related to research using cord segments. He stated that the proposed studies would provide valuable information and should be conducted as soon as possible.

Dr. Kurtzberg asked Dr. Andromachi Scaradavou to present her research on behalf of the New York Blood Center's National Cord Blood Program (NCBP). She began by stating that the NCBI defines a high quality CBU as one in which all critical steps, from collection to infusion, have been performed under optimal conditions so that the CBU has a high probability of engraftment.

Dr. Scaravacou outlined the steps in the CBU banking process, including collection and transport, processing, and cryopreservation. She noted that the NCBP believes that cord blood collection, maternal consent, and labeling are best done by dedicated, specially trained personnel who are not part of the delivery room staff. Dr. Scaradavou emphasized that the time from collection to completion of processing should not exceed 36 hours, and it is essential to maintain a constant temperature while the unit is being transported.

Since August 2006, the New York Blood Center has used an automated processing system that volume depletes the unit and separates the different components in a closed, sterile environment. The system can process 50 or more units per day, with processing information downloaded automatically into the database.

Dr. Scaradavou presented data comparing mononuclear cell recoveries, CD34+ cell recoveries, and CBU mononucleated cell (MNC) count for manual versus automated processing of CBUs. The data showed that the ratio of MNCs to TNCs in a CBU is about 0.47. Based on this ratio, an NCBI-eligible unit with a TNC of 900 million or more would have an equivalent MNC of about 425 million. About 66 percent of the units processed through the automated system exceed the cutoff of 900 million for TNC. However, 88 percent of the units have an MNC of 425 million or greater. Dr. Scaradavou stated that using a different measure for equivalent cell dose would result in a significant increase in the number of eligible units.

Dr. Scaradavou discussed the BioArchive controlled-rate freezing system that NCBP uses for cryopreservation. She presented a graph of the freezing curves for more than 300 units. There was very little deviation between the curves, proving that, with the BioArchive system, the freezing process can be standardized and is reproducible. Based on this finding, NCBP now requires the freezing curve for each unit to match the standard set by the research before the unit can be released to inventory.

Referring to testing, Dr. Scaradavou reiterated that the CFU assay is currently the only functional assay that is available. However, it has limitations because it is operator dependent, it cannot be repeated, and it requires a 14-day interval. Dr. Scaradavou presented data from a recently published NCBP study that combined the traditional CFU assay with staining and a computerized system that produces high-resolution digital images. Dr. Scaradavou stated that the stain enhances detection of the cells, without disrupting the colony. The stored digital images can be studied at a later date and standardized. She presented examples of the digital images and a graph showing a high degree of correlation between the CFU colonies and the CD34 counts of more than 2,000 units.

Turning to a discussion of segments, Dr. Scaradavou stated that evaluation of a thawed segment can reflect the quality of the CBU if, and only if, the segment was cryopreserved in the same way as the CBU. This raises questions about different methods of cryopreservation at different banks and the utilization of segments for release criteria. Dr. Scaradavou presented data from a current prospective study comparing pre-freeze and post-thaw CD34 of units and segments from those units, and comparing post-thaw CD34 and post-thaw CFU from those segments. Preliminary findings indicate that the pre-freeze CD34 viability for a unit and segment are virtually identical (99 percent versus 96 percent).

Dr. Scaradavou described the double-wall CryoShipper that her bank uses to ship units to the transplant center. The container absorbs liquid nitrogen and can maintain a temperature of –150 degrees for five to seven days, provided that it is not tipped. NCBP has introduced a device for continuous temperature monitoring during transport. When the device is returned to the bank, the data can be downloaded to document the temperature during the transportation process.

Dr. Scaradavou concluded by emphasizing that all steps of the process can affect quality of the unit and must be conducted under optimal conditions.

Discussion

Dr. Broxmeyer asked about the accuracy of the automated imaging system. Dr. Scaradavou stated that two types of comparison showed strong a correlation. Dr. Broxmeyer and Dr. Rubinstein discussed technical issues pertaining to the shipping container, including weight and cost of the unit and security issues.

Dr. Kurtzberg stated the steps that Dr. Scaradavou outlined would be part of the accreditation and licensing standards. However, even when banks pay attention to all of the details, some units are more viable than others. It is time for a serious prospective study to determine what else is needed to assess viability. Dr. Blume asked Dr. Kurtzberg what the next steps would be. She replied that, if the banks and the Council agreed, a protocol should be developed along the lines of what she described in her presentation. She noted that this had already been discussed with the research committee of NMDP, and a potential sponsor had been identified. A sample size is needed to proceed.

Dr. Pentz asked Dr. Kurtzberg if she had enough retrospective data to establish parameters to ensure that patients are not put at risk. She emphasized that it would be important to include such parameters in the protocol to ensure that ethical issues are addressed. Dr. Kurtzberg replied that many banks are conducting these assays informally, but this step is not currently part of the standardized algorithm for unit release.

Dr. Milford asked if there was a current standard of care, in terms of post-thaw criteria, for accepting a unit. Dr. Kurtzberg replied that there is none at the present time.

Dr. Anasetti noted that cryopreservation and post-thaw assessment were critical for stem cell transplantation, most obviously for cord blood. He asked whether any Government funding would be provided to develop cryopreservation protocols and post-thaw assessment. Mr.

Aronoff stated that he did not know where the money would come from in HRSA. Dr. Harvath stated that NIH's National Heart, Lung and Blood Institute (NHLBI) has an ancillary study request for application (RFA) that is open to anyone conducting on-going clinical trials that are funded through the NHLBI, such as the blood and marrow transplant network. NHLBI is also willing to meet with any investigator who would like to discuss a potential study in order to identify a mechanism to support the research.

Dr. Rubinstein stated that NCBP has shipped thousands of units for transplantation. There is a consistent pattern of issues that affect the viability of the transplant. The challenge is to identify and develop assays that can determine viability prior to shipment. This will require banks to change their procedures. It may also require interaction with transplant centers, so that the assay can begin while the patient is being conditioned. Dr. Rubinstein emphasized that if a bank has any indication that a unit is not viable, it should not be shipped.

Dr. Broxmeyer stated that variability has always been a problem for the CFU assay. Digital imaging helps to control for variability between centers, but it does not remove variability that occurs due to set up of the assay. Dr. Rubinstein noted that standard deviation predicts a 10 percent error. Dr. Kurtzberg stated that there are many variables in the sample itself. It is difficult to know how many cells are in the sample. Dr. Read stated that the denominator is as important as the numerator. If you only plate or count viable cells, the denominator is not accurate.

Dr. Blume encouraged Dr. Kurtzberg to bring the experts together, develop a proposal, and find an agency to support this important work.

Dr. Appelbaum stated that it would be invaluable for transplant centers that have saved segments to conduct a rapid, retrospective study that could help to identify parameters that determine viability of CBUs. He suggested conducting a survey to determine how many transplant centers have saved segments.

Specifications for NCBI Cord Blood Bank Accrediting Organizations: Final Draft
Cord Blood Bank Accreditation Organization and Recognition Process Work Group

- *E.J. Read, MD*

Dr. Read presented the revised draft of the specifications for accreditation. The document sets forth the purpose and objectives of accreditation and presents specifications for the organization of cord blood banks and all aspects of the CBB accreditation process, including standards compliance monitoring, CBB processes, collection sites, quality management, training, medical director, release of CBU to transplant centers, and outcomes data monitoring. The complete document is provided as an attachment to these minutes.

Dr. Read noted revisions to the following items:

- 2. b (ii): Dr. Read stated that this item was modified to make it less prescriptive regarding the need to show how inspection was conducted for all standards. The intent was to achieve a consistent approach to evaluating compliance with all standards. The

modified language also includes methods for an annual interim report, such as bank self-assessment and a dialog between the bank and the accrediting body.

- 2c. Collection Sites: Dr. Read stated that the two potential accrediting organizations had different approaches to this issue, and one of the organizations asked for additional guidance. She suggested that this item could be brought back to the Council for further discussion, if necessary.
- 2g. Release of CBU to Transplant Centers: The first sentence was modified to reflect the fact that NMDP is responsible for qualifying transplant centers for cord blood requests that it manages. The revised sentence reads: "The accreditation process must ensure that each cord blood bank has a mechanism for qualifying transplant centers to which the bank provides cord blood units, *when the cord blood request is not managed by the national coordinating program."*
- 2h. Outcomes Data Monitoring: Dr. Read highlighted the final sentence: "*The standards must specify the minimum frequency and types of data that must be collected."* She noted that the FACT standards discussed this issue in more detail than the AABB standards. Data monitoring presents challenges for all banks. Dr. Read suggested that this issue merited further review by the Council, the accrediting organizations, and HRSA.

Discussion

Dr. Milford identified three areas that were not addressed in the specifications: 1) record keeping, and to whom reports may be released, 2) appeals process for participating banks when they disagree with a determination, and 3) timing of re-accreditation if there is a change of ownership, location, or key personnel. Dr. Milford noted that, in the solid organ arena, the organ bank provides written approval before the accrediting organization can send the report. Dr. Read replied both accrediting organizations had standards for records. The process for submitting accreditation reports to HRSA would be part of the agreement between the accrediting organization and HRSA. With respect to appeals, Dr. Read stated that each of the accrediting organizations has procedures in place, and conflicts should be an administrative issue for HRSA. Mr. Aronoff stated that this issue could be resolved later and did not have to be part of the accreditation specifications. With respect to re-accreditation, Mr. Baitty stated that the NCBI contracts require banks to provide notification of any changes in ownership or key personnel. This was not tied to the accreditation process, but the accrediting organizations may have their own requirements in this area.

Dr. Kurtzberg asked what would be done to reconcile different inspection results if a bank is inspected by both organizations. Ms. Welte noted that NMDP policy stated that participating cord blood banks must be accredited by one, or both, organizations. That policy addresses the issue of discrepancies in accreditation decisions. Mr. Baitty noted that NCBI did not require banks to be accredited by both organizations.

Dr. Kurtzberg expressed concern that there were no mechanisms to provide access to reports in the event that an accreditation inspection identified serious deficiencies that the Council may need to address. Dr. Read replied that accreditation reports would be submitted to HRSA.

Important issues could come back to the Council, but the Council cannot take on oversight role. She noted that this could raise issues of confidentiality.

Dr. Hartzman referred to item 2g, regarding release of CBUs to transplant centers. He expressed concern that the document made CBBs responsible for determining whether transplant centers were qualified to receive products, without specifying criteria for making that determination. Dr. Read responded that the work group chose to give accrediting organizations the flexibility to set standards in this area. Council members engaged in a detailed discussion of how CBBs would make release decisions.

Dr. Blume called for any changes to the draft language. **A motion to approve the recommendation as drafted was made and seconded, and it was passed unanimously by voting members.**

Following the vote, Dr. Bowman suggested that the language of item 2a (ii) include a broader range of organizations whose requirements must be met, in the event of future reorganization of HHS. Mr. Aronoff stated that this could be addressed later. Mr. McGinnis suggested adding the phrase, "and other Federal requirements." The Council did not take any action to modify the statement.

Dr. Blume noted that Dr. Hartzman was still concerned about the language of item 2g. Dr. Pentz moved to modify the first sentence to read: "The accreditation process must ensure that each cord blood bank *adheres to* a mechanism for qualifying transplant centers to which the bank provides cord blood units, when the cord blood request is not managed by the national coordinating program." The motion was seconded and passed.

Dr. Read noted that the draft specifications, as revised and approved by the Council, would be submitted to the two accrediting organizations for review.

Cord Blood Bank and Peripheral Blood Stem Cell Post Licensure Issues

- *Donna Regan, ACBSCT Member and Executive Director, St. Louis Cord Blood Bank/Progenitor Cell Laboratory*

Ms. Regan stated that the purpose of her presentation was to discuss questions related to licensure issues, present a scenario of the future, and understand the challenges of the post-licensure environment. She noted that cord blood bankers are clinicians who are involved in a new paradigm of drug manufacturing. Cord blood products are available for a variety of therapies, and there are many new applications for these products.

Cord blood products are currently classified as Investigational New Drugs (INDs). CBBs are now charged with licensing their IND products through the FDA Biologic License Application (BLA). Licensure is a complex process that will involve the bank's business, financial, and legal departments. CBBs will need to develop a business plan and identify a license holder for each product.

Ms. Regan discussed current operational protocols and noted that some of these activities will need to be handled by a quality control unit. The requirement to meet Good Manufacturing Practices (GMP) may result in increased costs if banks go beyond what is set forth in the licensing guidance.

Ms. Regan stated that she considered an IND as a pathway to licensure. She raised questions about the licensing process: Would the IND cover all of a bank's nonconforming products? Can banks adopt a perpetual IND? Ms. Regan thought it unlikely and expressed concern that the FDA would eliminate the cost recovery portion of an IND if a bank did not demonstrate due diligence in submitting a BLA. She speculated that CBBs might consolidate due to some of these requirements.

Ms. Regan noted that cost recovery is currently designed to cover the four components of an IND (manufacture, development, shipping, and handling). She asked whether the agency fees associated with licensure of drugs would be applied to CBB licensure, and if there would be yearly establishment and product fees. She noted that it was unlikely that hospitals, academic centers, or blood centers would have the resources to absorb those costs.

Ms. Regan identified potential challenges during the transition period. She noted that it would be difficult for the FDA to review licensure applications from all of the NMDP banks. During the transition process, some products will be licensed, and some will not. Some unlicensed products will be shipped off-label and will require IND. Will the IND for those products be held by the bank, or by a transplant center that is using the product for an indication that is not included in the license? How will the new rules and processes affect transplant centers? Will they impede patient care? Ms. Regan noted that there would be financial implications if the guidance allows centers to charge more for licensed products. Pricing structures could affect product selection and, consequently, patient outcome. How will fees be paid post licensure? What models and other mechanisms will be available for reimbursement?

Ms. Regan noted that the inventories of most banks included products that had been processed differently over time, and she asked whether it is possible to demonstrate comparability. Some standard operating procedures have not been documented, and criteria have evolved through the years. Will variances be scaled? Ms. Regan noted that a bank's inventory may include a wide variety of products (e.g., licensed, off label, legacy, international), and she asked what would happen in the case of products that do not fit the BLA definition.

Ms. Regan noted that the field would continue to evolve, but banks would continue to be responsible for good patient outcomes. There will be new processing methods, new quality criteria, and new testing assays. What process would be put in place to amend the BLA to reflect those changes? Ms. Regan emphasized that banks need to manage their own internal changes and must also manage agency changes, including FDA and accreditation requirements.

Ms. Regan concluded by noting that AABB had approached FDA and other agencies to suggest that they conduct a workshop once the FDA guidance is finalized so that those in the field could come together to address the challenges.

Discussion

Dr. Read asked whether there was a target date for issuing the guidance. Dr. Lazarus said she could not comment on any aspect of the guidance until it was finalized. However, she informed the Council that her office was actively engaged in setting up an administrative framework so that could act quickly once the guidance is finalized.

Dr. Jeffrey McCullough of the University of Minnesota commented on the mixture of inventories. He noted that a review of quality criteria for 275 of cord blood units that the university received for transplants found that most of the units had one or more quality deficiencies. He expressed concern that the quality of unlicensed units could be questionable. Dr. Lazarus cautioned that licensure should not be correlated with quality—some unlicensed units could be as robust as licensed units. She acknowledged that it would be difficult for transplant centers to make the determination. Dr. McCullough said he would welcome the opportunity to streamline some of the requirements to eliminate some that do not impact the quality of a unit for transplantation.

Dr. Kurtzberg noted a unit could be licensed for a certain clinical application, but unlicensed for others, which adds to the confusion. She also noted that units in a bank's inventory that are not licensed would continue to be distributed under INDs. She expressed concern that it would be difficult to establish a clinical protocol to obtain those INDs.

Regulatory Framework for HPCs

- *Ellen Lazarus, MD, Ex Officio ACBSCT Member, and Medical Officer, Division of Human Tissues, Office of Cellular, Tissue, and Gene Therapies, CBER/FDA*

Dr. Lazarus provided an overview of the regulatory framework for hematopoietic progenitor cells (HPCs). She began by noting that the HPCs that FDA regulates are regulated as human cells, tissues, and cellular and tissue-based products (HCT/Ps). They are not regulated as blood products.

Dr. Lazarus noted that some HPCs are regulated solely under section 361 of the Public Health Service (PHS) Act and are not subject to licensure. The criteria are: extent of manipulation (361 HPCs must be minimally manipulated); intended use (361 HPCs must be intended for homologous use); combination with drug or device (361 HPCs must not be used in combination); and systemic effect or metabolic activity. Dr. Lazarus said that all HPCs have a systemic effect or metabolic activity; 361 HPCs are from a related donor.

HPCs that do not meet the criteria for Section 361 are regulated as biologics under section 351 of the PHS Act. They are subject to IND regulations, Current Good Manufacturing Practice (CGMP) guidelines, regulations regarding labeling and advertising, and biologics licensure regulations (BLA). They must also be manufactured in accordance with HCT/P regulations. By comparison, the regulations for section 361 HCT/Ps are narrower in scope than CGMP and are intended primarily to prevent the spread of communicable diseases.

Dr. Lazarus presented a chart comparing the regulatory approach for section 361 cord blood, section 351 cord blood, section 361 peripheral blood stem cells (PBSC), and section 351 PBSC. The table outlined the applicable regulations for each product, stated whether it was subject to licensure, and provided examples of HCT/Ps in that category. Dr. Lazarus stated that the draft guidance was designed to streamline the licensure processes for unrelated cord blood products, which are regulated under section 351. She noted that regulation of PBSC was similar to that for cord blood, although enforcement of IND and BLA requirements for PBSC is currently on hold.

Discussion

Dr. Champlin asked Dr. Lazarus to clarify whether clinical indications for hematopoietic reconstitution, acute lymphoblastic leukemia, and hemoglobinopathies would require separate BLAs. Dr. Lazarus stated that the draft guidance included "treatment of hematologic malignancy" as the indication, based on data in the public docket. Individual banks could rely on clinical data in the public docket to support their application and would not have to provide data from their own clinical trials. There was extensive discussion regarding the relative narrowness of that indication. This was a subject of consideration for the final guidance. Public meetings were conducted to obtain additional data, which is now in the public docket; and the issue is now under consideration.

Referring to Dr. Kurtzberg's earlier comment, Dr. Lazarus stated that use of a product for indications that are not on the label is off-label use. She acknowledged that this happens frequently in the field of drugs, and she expected that it would also be common in biologics. An IND would be required if the off-label use was associated with a clinical trial. Occasional use for treatment of an individual patient probably would not require an IND.

Dr. Milford referred to the Council's public and fiscal responsibility. He noted that licensing entails costs. He asked Dr. Lazarus to comment on the fiscal implications of licensing cord blood, and not peripheral blood stem cells. Dr. Kurtzberg noted that FDA cost recovery was now allowed for CBUs. She did not think that the market would bear any significant cost increase, even if licensure permitted it. Third-party payers may have a different view. Dr. Champlin noted that transplant doctors always look for the best unit. He would not disregard an IND unit if it was clearly superior to a licensed unit. Legacy units would continue to be in demand if they are the best match for recipients.

Mr. Sprague stated that the issues raised by Ms. Regan would have important implications for the patient community. He noted that the cord blood inventory has been increasing over the years, and he was concerned that some of those units would no longer be available for transplant. Mr. Sprague also expressed concern about the information that was presented regarding the quality of CBUs. He emphasized that patients put their lives in the transplanters' hands; the transplanters, in turn, rely on the banks. He hoped that the FDA's decisions would be in the best interests of the patient community. Ms. Regan responded that she did not think that the FDA intended to restrict the use of products. With regard to quality, CBBs are working hard to determine factors that impact quality. The banks are doing their best to minimize the risks of transplantation and do not ship units that might be compromised. They are also sensitive to the cost of this process.

Product Labeling Overview

- *Pat Distler, MS, MT (ASCP), SBB, Technical Director, International Council for Commonality in Blood Banking Automation, Inc.*

Ms. Distler provided an overview of ISBT 128, which is global coding and labeling system for blood, cellular therapy, and tissue products. The standard was developed for transfusion by the International Society of Blood Transfusion (ISBT) in 1994, following the first Gulf War. It was later extended to support cellular therapy and tissue products and has already been adopted by the Red Cross and Duke University.

The objective of ISBT 128 is to provide a standard information environment that supports the open movement of cellular therapy products around the world in such a way that critical information is communicated rapidly, accurately, and unambiguously. It also satisfies regulatory requirements for traceability and retention of information.

Ms. Distler noted that ISBT 128 is based on an information hierarchy that includes definitions, reference tables, data structures, delivery mechanisms, and labeling. Standard definitions of terms are the foundation of the system and provide a single nomenclature that is used around the world. Ms. Distler stated that ISBT 128 terminology is now required by FACT, the Joint Accreditation Committee, and AABB; and it will soon be required by NMDP.

ISBT 128 reference tables are combinations of defined terms that uniquely describe products or attributes. They provide a means of mapping definitions to codes that are suitable for electronic transmission. A set of international lookup tables provides a unique description of each product or attribute, a numeric code for the product, and a code for the product that is suitable for electronic transmission.

ISBT 128 data structures allow independent systems to communicate by providing technical definitions for data transfer and the context for information. The data structure for ISBT products consists of an equal sign, a percentage sign, and a four-character code. Computer programmers are aware of this requirement and build their programs around it.

ISBT 128 delivery mechanisms include bar coding, radio frequency ID tags, RSS codes, and electronic transfer of information between computers. The underlying elements (definitions, reference tables, and data structures) provide the required functionality to support these mechanisms.

ISBT 128 labeling creates a means of providing information in the right place and format. Ms. Distler emphasized the importance of ensuring consistency between electronic and eye-readable information. The standard label uses a four-quadrant model, with ABO/Rh in the upper right quadrant, expiration date and time in the lower right quadrant; product code in the lower left quadrant; and donor identification number and collection date in the upper left quadrant. All information is presented in both bar code and alphanumeric format. Not all information is required, but if it is included in the label it must be in the proper quadrant.

Ms. Distler described the global donation identification number, which consists of four elements: a unique facility or registry identification code assigned by the International Council for Commonality in Blood Banking Automation (ICCBBA); a two-digit year indicator; a six-digit sequential number; and a flag character. The final character of the code is a manual entry check character.

Ms. Distler noted that the ISBT product code database provides an international reference table of products. It includes clear, unambiguous definitions, with a structured presentation of information using concepts of class, modifier, and attributes. Regular updates are published by ICCBBA.

The key elements of ISBT 128 are the unique, global numbering system; standard data structures and formats for information allow for interoperability across systems. It is based on an international product list, definitions, and codes; and mechanisms are in place for the development and maintenance of the standard.

Ms. Distler outlined the cost to implement ISBT 128. These include a minimal payment to ICCBA, including a nominal annual licensing fee; bar coded labels or printers; bar code readers; software; and labor costs for validation, development of standard operating procedures, and training. She noted that software was the most expensive portion of the product.

ISBT 128 has many advantages. It improves communication through the use of globally standardized, easy-to-read labels that overcome language barriers; it improves traceability through the use of bar codes and a globally unique identifier; and it meets requirements of standards and regulations wherever the products go.

Ms. Distler presented maps showing the countries that have made a national decision to use ISBT 128 for blood and the locations of registered facilities around the world. She noted that both Canada and the U.S. have decided to use ISBT 128 for blood. The accrediting organizations for cell therapy in Europe and North America have decided to use the terminology at this point and are likely to adopt the bar codes at a later date.

The role of ICCBBA is to develop and maintain the standard, with the support of advisory groups. It is also responsible for the assignment of new codes, technical support, educational material and promotion of the standard.

Discussion

A member of the audience asked how many centers represented in the Council were using the code. Dr. Read and Dr. Kurtzberg said that their facilities use it. Ms. Regan said that her bank would begin to use the system on January 1, 2009. Dr. Rubinstein stated that his bank had used bar codes for many years, but it had not implemented ISBT.

Dr. Sims stated that there appears to be need for a uniform type of coded information regarding what the unit is, and how it has been processed. Ms. Distler stated that people have requested special codes. She will bring this up with the advisory committees.

Dr. Rizzo stated that the availability of a standard label that is truly unique and global makes it possible to get reports to the right people regarding the outcomes of product use. Ms. Distler added that the standardized label means that data managers no longer have to customize systems.

Dr. Read asked whether there were any special issues associated with the ability of transplant centers to read the labels. Ms. Distler stated that AABB required U.S. hospitals to use ISBT 128 for blood as of May 1, 2008. The goal is to enable scanning to be performed at the patient's bedside. Ms. Distler noted that if a product is converted in a laboratory, it gets a new label.

Goals of Incoming Chairman of the NMDP Board

- *Edward L. Snyder, MD, Chair-Elect, NMDP; Professor Laboratory Medicine, Yale University*

Dr. Snyder introduced himself to the Council and noted that he had been a member of the NMDP board since 1999. After reviewing the NMDP mission statement, he stated that 2008 was a year of growth for the organization. There was a 10 percent increase in adult donor and cord blood recruitment, with 400,000 new adult donors added to the registry, half of whom were minorities. Transplants increased by 18 percent overall, with a 21 percent increase in transplants for ethnic minorities and a 46 percent increase in cord blood transplants.

Dr. Snyder presented graphs illustrating the growth of the registry and the number of NMDP facilitated transplants over the past 20 years. He noted that in 2008, cord blood transplants exceeded bone marrow transplants by 20 units. A graph of transplants by race since 2003 showed large, steady increases in transplants among African Americans and Asian/Pacific Islanders. Hispanic and American Indian populations have had smaller rates of growth. Dr. Snyder emphasized that NMDP is dedicated to ensuring that patients of all races and ethnicities needing a transplant will be able to get one.

Dr. Snyder outlined NMDP's goals for 2009. The adult donor recruitment goal is 460,000, half of which should be minorities. The cord blood recruitment goal is 30,000. Dr. Snyder noted that the board holds NMDP management accountable for meeting these goals. NMDP will launch its new "Be the Match" brand for donor recruitment and fund raising to increase awareness of the program. The Donor Management Performance System, which is a method of identifying best practices, will set new goals and reward donor centers that improve donor availability and timeliness of donor management. NMDP will also develop and test a new system for search management to improve the donor management process and improve service to the transplant center.

Dr. Snyder presented the primary goals for his term as Board chair:

- Reauthorization of the Congressman C.W. "Bill" Young Cell Transplantation Program
- Evaluate the infrastructure in the U.S. to accommodate the goal of 10,000 transplants by 2015
- Reauthorization (and funding) of the BMT Clinical Trials Network for another 5-year cycle
- Support CIBMTR programs at the Board level (improve outcomes)

- Support science aimed at determination of the best cell source for transplantation
- Ensure robust communications between the Board and management
- Ensure a strong network with "user-friendly" communications
- Strengthen relationships with NMDP's international partners
- Continue toward the goal of obtaining an HSCT for all in need

Announcements

Dr. Blume noted that a new work group would be formed to address the process of informed consent. Members would include Dr. Pentz, Dr. Sims, Dr. Yim, Ms. Stewart, Ms. Regan, Dr. Milford, Dr. Bishop, and Dr. Callender.

Dr. Blume announced that HRSA would send the recommendations on MDS and confidentiality to the Secretary and would forward the draft specifications to AABB and FACT**,** asking them whether they can/will comply with the specifications.

Dr. Blume stated that he was looking forward to receiving a proposal for a study of lab procedures to identify viable cord blood products. He polled members regarding their availability to meet on May 4-5 rather than May 12-13. Dr. Kurtzberg noted that those dates would conflict with a major professional meeting. The next Council meeting was therefore confirmed for May 12-13, 2009.

Updates from the Center for International Blood and Marrow Transplant Research (CIBMTR)

Effect of Dose on Minority Cord Blood Transplantation Patients

- *Mary Eapen, MD, MS, Associate Scientific Director, CIBMTR MKE Campus*

Dr. Eapen presented research on outcomes after cord blood transplantation that focused on cell dose, donor-recipient HLA disparity, and minorities. She noted that the importance of donor-recipient matching for unrelated donor bone marrow transplantation was well described in the literature. Risks of graft failure, graft vs. host disease (GVHD), and mortality are higher, and increasing numbers of mismatch progressively worsens overall survival, with each additional mismatch lowering the probability of survival by 9-10 percent.

Dr. Eapen noted that placental blood lymphocytes are less alloreactive. This unique feature has allowed successful transplantation of cord blood units with degrees of donor-recipient matching that would be considered prohibitive with unrelated adult donors. Approximately 10,000 cord blood transplants have been performed worldwide. Sixty to 70 percent of the recipients were children with malignant diseases.

Dr. Eapen stated that 85 to 95 percent of cord blood transplants are mismatched at one or two loci. The standard criteria for cord blood transplantation are HLA-A and -B (intermediate resolution) and allele-level -DRB1. Allele-level HLA typing at -A and -B and matching at HLA-C are not routinely considered.

Dr. Eapen reviewed a CIBMTR study that compared outcomes for children who received cord blood transplants for acute leukemia with outcomes for children who received bone marrow transplants between 1995 and 2003. The criteria for bone marrow selection was based on current standards of 8/8 match or mismatch, with allele-level typing considering HLA-A, -B, -C and -DRB1. The standards for cord blood transplantation were -A and -B at low resolution and -DRB1 at the allele level. Only seven percent of the transplants were matched in the cord blood population. Forty percent were one-locus mismatched, and 53 percent were mismatched at two loci. Sixty percent of the patients were Caucasian. The median cell dose was $5x10^7$/kg.

The study found that neutrophil recovery was lower for patients who received mismatched cord blood transplants. The treatment-related mortality rate for those patients was higher for cord blood recipients during the first 3 months, but for patients who survived the first 120 days, the mortality rate was similar to that for matched bone marrow. The risk of mortality was about 1.5 times higher for non-Caucasian patients, including those who received matched bone marrow.

Dr. Eapen then reviewed a more recent study that looked at transplant data from 2000-2007 for over 700 patients, 80 percent of whom had a hematological malignancy. The median age was 7 years. All patients received a single CBU, but the median cell dose was higher. The researchers found that rates of hematopoietic recovery, overall mortality, and overall survival were virtually identical. Based on the data, there was general agreement that for hematological malignancies, a TNC of $3x10^7$/kg (pre-freeze) was probably adequate. However, Dr. Eapen noted that the data should probably be reviewed based on the information presented by Dr. Kurtzberg and Dr. Scaradavou.

Dr. Eapen stated that 40 to 45 percent of CB transplants are mismatched at two loci. There are two questions that remain: Can you apply what has been observed in pediatric malignancies to the non-malignant setting with younger patients? Is there an optimum cell dose above which the negative effect of a two-locus mismatch can be overcome as has been shown with one-locus mismatched transplants? Dr. Eapen stated that this was the focus of a study that CIBMTR was currently conducting in collaboration with the Eurocord registry.

Dr. Eapen noted that some researchers have suggested that an incremental increase in cell dose may increase survival, but this has not been proven conclusively. Higher rates of neutrophil recovery have been observed with CBUs which are 4/6 matched and TNC of $5x10^7$/kg or higher, but this does not correlate with any survival advantage.

To determine the effect of HLA disparity and cell dose for non-malignant diseases, Dr. Eapen summarized the results of several studies, including a Duke University study on CB transplants for metabolic diseases. The patients were much younger, with a median weight of 12 kg and a median cell dose of nearly $10x10^7$/kg. In the Duke study, neutrophil recovery was associated with a higher CD34 and CFU counts. Survival was influenced by performance score, CFUs, and donor-recipient ethnicity mismatch. A European study of the role of transplantation in immunodeficiency disorders found that higher cell dose was associated with greater neutrophil recovery. A multivariate analysis found that the rate of mortality was 2.5 higher for patients who received a transplant that was mismatched at two or three loci. Dr. Eapen also presented data from a study of transplant outcomes for patients with Fanconi anemia. The study found that

TNC dose of $5x10^7$/kg or higher was associated with greater neutrophil recovery. HLA disparities were associated with increased risk of transplant-related mortality.

Dr. Eapen summarized her presentation by stating that cell dose is important. The minimum required for hematological malignancy is $3x10^7$/kg, with higher doses required for some non-malignant diseases. CD34 dose is also predictive of outcome. The effect of race and ethnicity on transplant-related mortality is independent of cell dose and donor-recipient HLA match.

Discussion

Dr. Milford asked whether there were any data showing that donor race was a factor in survival rates for cord blood transplants, independent of the race of the recipient; and whether the differences Dr. Eapen observed were due to any differences in hematopoietic recovery versus relapse, in malignant diseases, and lack of relapse as an issue in non-malignant diseases. He also commented that he was unsure whether the HLA effect was apparent in race differences, since transplant criteria only look at HLA-A and -B at intermediate resolution and do not consider HLA-C. Dr. Eapen replied that her prior research focused on recipient race and did not look at donor race, specifically. However, she would look at that more closely in the future. She stated that the impact of HLA disparity on transplantation needs further study. In an analysis of recent umbilical cord blood transplants, we did not observe an effect of HLA mismatch on survival. Mismatched transplants affect hematopoietic recovery. Hematopoietic recovery and survival could be associated with multiple factors including cell dose of the unit and presence of HLA antibodies as demonstrated by Drs. Bray and Anasetti in their recent report on the association of HLA antibodies after unrelated adult donor transplants.

Mary Horowitz stated that it would be difficult to answer such questions until there have been a sufficient number of transplants. There is a great amount of "background noise" in mismatched transplants, making it difficult to determine what factors are involved. In bone marrow transplants, antigen versus allele-level mismatching does make a difference.

Dr. Champlin asked whether there were many 6/6 matched adult patients. Dr. Eapen stated that the rate was between three to five percent. The pediatric data suggest that there is an advantage to transplanting patients with a 6/6 match cord blood unit.

Dr. Lubin asked whether there were any data on combined bone marrow and cord blood transplants. Dr. Eapen stated that there were some cases, but no conclusive studies.

Dr. Rubinstein noted that multivariate analyses seemed to weaken the association, yet some effects can be seen. This means that the effect is quite strong. Dr. Horowitz stated that HLA was clearly important; it is a question of which loci had the greatest impact. She suggested that the race effect may be due to an uncharacterized mismatch. Dr. Rubinstein suggested that this would be known before long.

Dr. Appelbaum stated that he had conducted a case controlled study of double cord transplants, compared to bone marrow transplants and matched and mismatched unrelated transplants. The study found that the risk of relapse for double cords was significantly less than for matched

unrelated transplants. He did not think that the role of HLA would be understood soon, given the many disease categories and the numerous elements that factor into matching.

Dr. Milford noted that hemoglobinopathies are prevalent among African and Mediterranean communities. Recent data suggest that children who are transplanted early have a much higher success rate. He suggested that it would be extremely important to pursue that avenue. Dr. Horowitz noted that the BMT CTN recently opened a Phase 2 study of unrelated marrow or cord blood transplants for children with sickle cell disease.

Center-Specific Analysis for Blood Stem Cells

- *Doug Rizzo, MD, MS, SCTOD Project Director, Associate Scientific Director, CIBMTR MKE Campus*

Dr. Rizzo began by reminding the Council that one purpose of the SCTOD was to analyze and report on center-specific outcomes for related and unrelated donor transplants. The report is to include an analysis of HCT survival rates overall, as well as unadjusted 1-year survival rates by center for various age and disease categories. Most importantly, the SCTOD is to analyze the 1-year, risk-adjusted survival for each U.S. center, compared to normative data.

The SCTOD is to report rates of survival for related HCT recipients separately from those of unrelated recipients; to distinguish rates of survival for recipients of umbilical cord blood from recipients of other types; and to report on single versus multiple cord unit Hats. SCTOD is also to present aggregate survival rates and comparisons between HCT using HRSA-funded cord blood units and national survival rates for all cord blood units.

Dr. Rizzo stated that the initial design and subsequent changes to the outcomes reports would be reviewed by clinical and statistical experts and transplant centers; and the approach and methods report would be approved by HRSA. SCTOD reports would be disseminated to the public through the hrsa.gov Web site and printed material, using plain language principles where possible.

Dr. Rizzo noted that NMDP had performed center-specific outcomes analysis regularly since 1994. The challenge for CIBMTR, as the new contractor, is to continue the annual assessment of center-specific outcomes for unrelated donor transplants and add related-donor transplants in 2010. CIBMTR intends to engage the transplant community, other experts, and the public in its efforts and to launch an active research program to identify the processes and resources that determine performance.

To launch this effort, CIBMTR hosted an interactive meeting in September 2008 that brought together HSCT physicians, members of the ASBMT Qualitative Outcomes Committee, statisticians in HSCT and other fields, experts from the Solid Organ Program and general medicine, along with patients, payors, and representatives of HRSA and NIH. The forum included presentations on background issues, a panel discussion on implications of the research, and breakout sessions to discuss statistical modeling, outcome measures and sample constraints, the process for model review and change, avoiding unintended consequences, transitioning to all allogeneic reports, and methods for reporting results.

Looking ahead toward 2010, CIBMTR will issue a report on the recommendations from the Forum. It will develop a draft plan for conducting the center-specific outcomes analyses and will present the plan at the 2009 BMT Tandem meetings. After incorporating Tandem feedback, CIBMTR will present the draft plan to HRSA and the ACBSCT for review. Once the finalized plan is published, CIBMTR will conduct the center-specific outcomes analyses and prepare its report.

Discussion

Council members did not have any comments or questions.

Adult Donor and Cord Blood Inventory Registry Models

- *Dennis Confer, MD, Chief Medical Officer, NMDP, Associate Scientific Director, CIBMTR MSP Campus*
- *Martin Maiers, Director of Bioinformatics, NMDP*

Dr. Confer and Mr. Maiers described the NMDP's efforts to develop a matching model using data from the adult donor registry. Dr. Confer began by presenting a graph showing a ten-fold increase in the adult donor registry. The vast majority of donors have been HLA typed, and virtually all donors in the registry have now been typed by DNA. There are nearly 92,000 CBUs in the registry, nearly all of which have been DNA typed. NMDP plans to increase the registry by 460,000 adult donors in 2009 and increase the cord blood inventory by 30,000 units. One purpose of this expansion is to address attrition, but the other reason is to increase the likelihood of matches.

Dr. Confer conducted an analysis of the registry to determine how match rates would change as the registry grew. The study was conducted under the previous SCOTD contract. The key to the task was to refine match projections so they would accurately reflect registry growth.

Dr. Confer stated the lack of high-resolution data on allele and haplotype frequencies, combined with a lack of detailed information on donor race and ethnicity, presented significant challenges.

Mr. Maiers described the researchers' efforts to increase the resolution of adult donor matching. The research was based on a 1995 study that looked at the impact of racial genetic polymorphism on the probability of finding an HLA-matched donor; a 2004 study on the optimal size and composition of the national registry of stem cell donors; and a 2008 study on the use of cost-effectiveness analysis to determine inventory size for a national cord blood bank.

Mr. Maiers described the three steps of the matching model: 1) determine the frequency of an HLA type within the registry, 2) determine the expected match rate for an individual, and 3) determine the overall match rate for a population. Haplotype frequencies are the key to this model. Because the distribution of HLA frequencies in the U.S. population is unknown, they must be estimated from a population sample. The existing registry is the best source for these population estimates.

Using registry data, the researchers conducted high resolution HLA typing of a random sample of three groups of minority adults in the registry (African Americans, Hispanics, and Asian/Pacific Islanders). Using a matching algorithm (HapLogic-II), they assigned an 8/8 allele match probability for each potential match and computed the conditional probability that additional typing would reveal an 8/8 allele match.

Mr. Maiers presented a graph showing match rates generated using the registry model compared to 2008 benchmarks based on actual searches. The comparative data were shown for the three minority groups, plus a group of Caucasian bone marrow donors. Mr. Maiers noted that the projected match rates generated by the registry model were significantly higher than the benchmarks for all groups. The gaps were greatest for African Americans and Asian/Pacific Islanders. These discrepancies indicated that the model must be further refined.

The researchers are in the process of developing a more sophisticated tool to generate haplotype frequency estimates. Efforts are also underway to obtain more detailed population data by analyzing racial/ethnic subgroups independently, incorporating theta analysis and unsupervised clustering. Mr. Maiers presented data from an interim draft report, which showed that match rates generated by the new model were closer to the benchmark data.

Mr. Maiers presented a timeline for completion of the project, including a full registry-size projection model and report in March 2009, ongoing research into unsupervised population clustering, and a clinical validation study.

Discussion

Dr. Champlin noted that this is very complicated work, but it is important to determine potential matches for each donor. He asked whether it would be possible to determine how many additional matches would be possible for each million donors added to the registry. Dr. Confer stated that we now have a more sophisticated definition of match, but projections are still difficult without more high-resolution data. Mr. Maiers noted that the terms “allele” and “high resolution” were not clearly defined within the field.

Dr. Anasetti commented that the benchmark data were disappointing. The match rate was 50 percent 15 years ago; and it is disappointing that the situation has not improved. Mr. Maiers stated that the goal of the clinical validation study is to get an unbiased, observational standard. He described the methodology of the validation study and clarified how that differed from the process used to develop the benchmark. Dr. Champlin thought that a study with real patients would be a better use of resources. Dr. Confer described the logistical challenges of conducting a study of that type.

Dr. Rubinstein noted that, in the cord blood scenario, there are two potential subjects, the donor and the mother. He suggested conducting a study of donors and mothers at one site, compared to another.

Public Comment

There were no public comments.

Dr. Blume adjourned the meeting at 3:23 p.m.

ATTACHMENTS

- Recommendation on Allogeneic Stem Cell Transplantation for Myelodysplastic Syndromes (Approved by ACBSCT on 12/15/08)
- Confidentiality Table (Approved by ACBSCT on 12/15/08)
- Draft Specifications for NCBI Cord Blood Bank Accrediting Organizations (Approved by ACBSCT on 12/16/08)

Recommendation on Allogeneic Stem Cell Transplantation for Myelodysplastic Syndromes

- Myelodysplastic Syndromes (MDS) and acute myeloid leukemia (AML) are life-threatening blood disorders that are often part of the same disease process continuum.
- There is strong evidence for the benefit of allogeneic stem cell transplantation in the treatment of AML.
- There is strong evidence for the benefit of allogeneic stem cell transplantation for MDS in patients less than 65 years, and growing evidence in patients greater than 65 years.
- There is also evidence that co-morbidities may have a greater impact than age on allogeneic stem cell transplantation outcomes in older adults.

Based on these findings, the ACBSCT endorses consideration of the use of allogeneic stem cell transplantation for MDS and recommends that the Secretary instruct CMS, as a high priority, to develop an appropriate strategy for NCD.

Approved by ACBSCT, December 15, 2008

CONFIDENTIALITY TABLE

Year CBU collected	X		
Donor Sex	X		
ABO/Rh	X		
TNC of CBU	X		
HLA of CBU: Level and location of match/mismatch to any cord blood candidate and allele-level typing to any cord blood recipient	X		
Abnormal findings that include positive IDM results, which may make the CBU "ineligible" by FDA standards, though still clinically useable	X		
Abnormal findings that include risk re: Maternal Health History Questionnaire	X		
Abnormal findings that include genetic hemoglobin abnormalities	X		
Whether or not the unit is foreign or domestic		X	
Name of CB Bank where CB Unit is stored		X	
Code identifying CB Bank		X	
Collection date of CB Unit		X	
Collection month of CBU		X	
Status of donated CBU (stored, discarded, used for research or transplant)		X (to donor)	
Donor Race		X	
Donor name or contact information			X
Recipient name or contact information			X (to donor)

*in a clinically appropriate manner, or in greater detail upon patient request

Approved by ACBSCT, December 15, 2008

DRAFT Specifications for NCBI Cord Blood Bank Accrediting Organizations

Purpose: The purpose of these specifications is to define minimum criteria for an accrediting organization to be recognized for the accreditation of cord blood banks participating in the National Cord Blood Inventory (NCBI), C.W. Bill Young Cell Transplantation Program.

Objective: The objective of HRSA is to recognize, using recommendations from the ACBSCT, one or more accrediting organization(s) that will ensure that cord blood banks accredited by their program(s) maintain high quality operations that are compliant with established standards and NCBI requirements, as specified by HRSA, throughout the accreditation period.

Specifications

1. Organizational Structure: The cord blood bank accreditation program must be an established program for the inspection and accreditation of cord blood banks and their associated cord blood collection facilities. The accreditation program must ensure that accredited cord blood banks consistently operate in a high quality manner and provide high quality products for patient transplantation.

1a. The accreditation program must have a comprehensive approach to accreditation including established policies and procedures for the development and implementation of standards and on-site inspection of facilities, including collection sites.

1b. The accreditation program must have a consistent and thorough process for review of inspection reports. This review must include an oversight procedure for approval of accreditation to ensure consistency and objectivity. The oversight should be through a designated committee or other similar formal structure.

1c. The accreditation program must assess/inspect against established standards that are developed through consensus by a panel of experts from the blood stem cell transplantation community, including those with specific expertise in public cord blood banking for unrelated donor cord blood transplantation.

1d. The accreditation program must have a mechanism to ensure a consistent and integrated approach exists for compliance with standards within all major components of the cord blood collection and banking process. At a minimum, major components include cord blood collection sites and cord blood bank processing and storage sites.

1e. The accreditation program must have specific qualifications and a formal training program for inspectors. Inspectors must demonstrate understanding of, and expertise in, the accreditation process and proficiency in areas they are charged to inspect.

1f. The accreditation program must have an established system to ensure fair and consistent inspection practices and consistent interpretation of standards.

1g. The accreditation program must include a quality monitoring system designed to evaluate and promote consistency and reproducibility across inspections. The accreditation program must have established procedures to manage problems discovered during the inspection process, including criteria for dismissal of inspectors.

1h. The accrediting organization(s) must provide regular progress reports to HRSA on the relevant accreditation issues, changes to the accreditation program, and accreditation status of NCBI banks.

2. CBB Accreditation

2a. Cord Blood Bank Standards Compliance Monitoring

2a(i). The accreditation program must assess ongoing compliance with standards/accreditation requirements at least annually, including an on-site inspection at least every two years. The system used to monitor compliance with standards/accreditation requirements should be based on established methods that ensure that accredited facilities continue to consistently provide high quality services and operations.

2a(ii). The accreditation program must take appropriate actions against cord blood bank facilities not meeting standards/accreditation requirements, HRSA requirements, and FDA requirements. If appropriate, these actions must include immediate changes in the bank's accreditation status from accredited to non-accredited.

2a(iii) The accrediting organization must have a system to provide HRSA with inspection reports of NCBI cord blood banks, and to notify HRSA of NCBI cord blood banks determined not to be in compliance with accreditation requirements, the actions taken with respect to the banks, and the corrective actions taken by the banks.

2b. Cord Blood Bank Evaluations

2b(i). At a minimum, the accreditation program must evaluate the following cord blood bank processes: donor education, screening and informed consent; collection of cord blood units (including associated sample collections); processing, testing and storage of cord blood units; cord blood unit selection for transplantation; cord blood unit release and shipment to transplant centers; and monitoring of post-thaw product quality assays and transplant outcomes.

2b(ii). The inspection process must ensure that each bank is consistently evaluated against all applicable standards and accreditation requirements. The inspection report must include description of what was evaluated and the methods used in the evaluation (e.g., bank self-reporting, record/document review, verbal discussion on-site, on-site observation. etc).

2b. The accreditation program must be willing to evaluate NCBI banks against specific HRSA NCBI requirements that may differ from, or exceed, requirements for non-NCBI cord blood banks. Additional fees, if any, associated with these additional inspection/accreditation activities, and reporting to HRSA, must be established and published prior to scheduling inspections, and will be borne by the NCBI cord blood bank.

2c. Collection Sites: The collection site must be evaluated as an integral part of the cord blood bank. The accreditation program must have an established procedure to determine the minimum number of collection sites that must be inspected to adequately assess the overall quality of the bank's collection activities.

2d. Quality Management: The accrediting organization's standards must require that accredited cord blood banks have a comprehensive quality management program that encompasses all operational aspects of the cord blood bank, and ensures that deviations and adverse events are monitored and reported to regulatory agencies, when appropriate.

2e. Training: The accrediting organization's standards must require appropriate education and training of all staff involved in the cord blood collection and banking process. At a minimum, the program's standards must ensure all staff receives task-specific ongoing training and regular competency evaluations. This includes personnel performing cord blood collection and processing tasks who work directly or indirectly (through agreements or other arrangements) for the cord blood bank.

2f. Medical Director: The accrediting organization's standards must require each cord blood bank to have a designated medical director for the cord blood bank and all facilities involved in cord blood bank activities. This includes, but is not limited to, collection sites, cord blood processing labs and storage facilities. The designated medical director for each banking or collection activity must be qualified to supervise and oversee all operations of that activity.

2g. Release of CBU to Transplant Centers:
The accreditation process must ensure that each cord blood bank adheres to a mechanism for qualifying transplant centers to which the bank provides cord blood units, when the cord blood request is not managed by the national coordinating program. The accreditation process must ensure cord blood banks provide appropriate instructions to transplant centers regarding thawing procedures and other pre-infusion steps for the cord blood units released.

2h. Outcomes Data Monitoring: The accrediting organization must have standards addressing how cord blood banks will monitor ongoing compliance with requirements for timely collection of data pertaining to post-thaw product quality assays and transplant outcomes. The standards must specify the minimum frequency and types of data that must be collected.