ACBSCT Advisory Committee
Rockville, MD
April 28 - 29, 2008

Monday, April 28, 2008

Welcome & Introduction

Dr. Blume welcomed the group and announced that the ACBSCT's various work groups have held 16 conference calls and communicated by email in order to move ahead on the topics identified at the last meeting. The agenda order was changed so that the HHS Ethics Office could make a short presentation.

Ms. Louise Wagner from the Ethics Office announced that the office had made determinations, based on the information provided by ACBSCT members, about which members needed to have a waiver and/or recusal. She stated that waiver letters had been issued stating that members' expertise outweighed their potential conflict of interest. She asked members to contact her with any questions or concerns.

Cord Blood Banks' Organization & Recognition Process

- *E. J. Read, M.D., Work Group Chair*
- *Karen Shoos Lipton, J.D., Chief Executive Officer, American Association of Blood Banks*
- *Phyllis Warkentin, M.D., Medical Director, Foundation for the Accreditation of Cellular Therapy and Professor, Pediatrics Hematology/Oncology, University of Nebraska*
- *Dr. Robert Soiffer, immediate Past-President, ASBMT*
- *Dr. Mary Laughlin, President-elect, International Society for Cellular Therapy (ISCT)*

Overview of Presentations -- E. J. Read, M.D., Work Group Chair

Dr. Read introduced the upcoming presentations and recapped the ACBSCT's January meeting. Both the Senate and the IOM reports mention the importance of cord blood bank (CBB) accreditation to ensure quality of cord blood units. Dr. Read summarized HRSA's presentation from January, noting that nearly all public cord blood banks are accredited by AABB, FACT, or both. In January, HRSA asked the ACBSCT to:

- Formulate a plan for developing recommendations to the Secretary and HRSA about accreditation covering: a recommended "recognition" process, criteria for "recognition," and expertise and backgrounds of individuals to be involved in HRSA's recognition decision;
- Execute the plan for developing recommendations; and
- Conduct information-gathering, including presentations by accrediting organizations.

The work group reviewed specifications for the two accreditation organizations and

asked them to present at the April meeting. At the meeting, the two accreditation organizations were expected to respond specifically to eight questions/requests. The objective was to recognize one or more accrediting organizations that will ensure that cord blood banks accredited by their program(s) maintain high-quality operations, which comply with established standards and NCBI requirements as specified by HRSA.

American Association of Blood Banks -- Karen Shoos Lipton, J.D., Chief Executive Officer, AABB

Ms. Lipton gave a background on the AABB and described the Association's standards program, which is independent from its accreditation program. The Standards Program Committee oversees the AABB Quality Management Subcommittee which, in turn, oversees each AABB program unit.

Ms. Lipton described the representation on the CT Standards Committee and the AABB's standards requirements. She noted that comprehensive standards apply to all cellular therapies, including HPCs, cord blood, pancreatic islets, and other somatic cells. Ms. Lipton also described the AABB accreditation program and the membership of the Accreditation Committee. AABB began conducting unannounced assessments last year, based on recommendations from the IOM.

Ms. Lipton described the cord blood assessment process and outcomes, including activities in the case of non-compliance, and she noted that the AABB investigates or analyzes every complaint it receives to evaluate whether there is a need to act.

The AABB anticipates that additional criteria will be required for the HRSA assessment, and it will prepare additional assessment tools for specific HRSA requirements (e.g. viability, CD34, specific cryopreservation time). In addition, the AABB will provide summary report(s) to HRSA. AABB proposed self-assessment in alternate years, to be reviewed by AABB professional staff to ensure consistency, and to be due one year from the last on-site assessment. Progress reports would address accreditation issues, accreditation program changes, accreditation status of NCBI banks, and additional reports as requested by HRSA. AABB is also interested in the ACBSCT considering whether there should there be independent accreditation of facilities that collect cord blood units.

In closing, Ms. Lipton expressed her belief that the existence of two different organizations that compete in a healthy manner has created synergy in the field and has been beneficial to the AABB's program. She concluded by stating that, if the ACBSCT recommended that there be a single organization, the AABB was committed to working with other bodies on this recommendation.

Foundation for the Accreditation of Cellular Therapy (FACT)

- *Phyllis Warkentin, M.D., Medical Director, Foundation for the Accreditation of Cellular Therapy and Professor, Pediatrics Hematology/Oncology, University of Nebraska*
- *Dr. Robert Soiffer, immediate Past-President, ASBMT*
- *Dr. Mary Laughlin, President-elect, International Society for Cellular Therapy*

(ISCT)

Dr. Warkentin provided an overview of FACT standards and its accreditation program. She noted that FACT also participates in processes to establish international standards with the Joint Accreditation Committee ISCT and EBMT (JACIE). Dr. Warkentin reviewed the standards-setting process, including FACT's Standards' Committee, the CBB Standards Subcommittees, and their memberships.

FACT-NetCord accreditation is based upon documented compliance with NetCord-FACT International Standards for Cord Blood Banks (current edition). The voluntary inspectors are experts in their fields. The Accreditation Committee reviews each report and determines next steps as well as accreditation status. Dr. Warkentin described the inspector qualifications, which she asserted set FACT apart. She described inspection outcomes and noted that every deficiency must be corrected before accreditation (the only exception was for longer-term corrections, in which planned corrections are accepted).

Dr. Robert Soiffer, the immediate Past-President of the ASBMT, represented the current ASBMT president (Dr. Helen Heslop). He stated that the ASBMT fully supported both FACT-NetCord standards for cord blood banks and FACT as the accrediting agency for CBB. ASBMT recommended that HRSA recognize a single accrediting organization, as recommended by the IOM. Doing so would avoid confusion that would be generated by multiple sets of standards or multiple accrediting agencies. ABSMT also encouraged HRSA to recognize FACT as the agency for setting standards and accrediting banks under the National Cord Blood Inventory program.

Dr. Mary Laughlin, the President-elect of International Society for Cellular Therapy (ISCT) noted that ISCT co-founded FACT with ASBMT. She stated that ISCT strongly endorses FACT as the organization for Standards and accreditation of cord blood banks under the National Cord Blood Inventory Program.

Discussion

Dr. Read thanked the speakers for the presentations and opened the discussion by referring to the draft specification (see handout). She welcomed members' comments on any particular specification and/or language. The group discussed the fact that the proposal limited the release of units to accredited CB transplant facilities, but noted there was currently no way for a transplant center to be so accredited. The work group members agreed that this section should be changed and asked members to provide their thoughts and alternative language in this area.

The group discussed transplant programs located outside the U.S. While the intent was that accredited CBB not sell units to "just anyone," the U.S. cannot regulate international facilities. The Joint Accreditation Committee-ISCT & EBMT (JACIE) does have international accredited programs and could be a mechanism for this process. A CIBMTR representative cautioned that 30 percent of cord blood exchange is international and that it is important not to impede international exchanges. The group also noted that

accreditation and other requirements should not be so onerous that facilities refuse to participate. In fact, Dr. Parkman reported that his agencies programs have stated that if the requirements are too onerous, they will not participate.

The differences between AABB and FACT can be rationalized. The use of paid versus volunteer assessors is a big difference. The FACT representative added that she believed that the acceptance of variance was another difference: in FACT's opinion, standards should be present and enforced; if there is no agreement on what the best thing is, there should be flexibility to meet the process. AABB clarified that such variances are only granted by the Standards Committee and there has never been a variance for cord blood units. AABB's philosophy is that if there are data to show that the same outcome is reached, the Committee may approve a variance.

The group discussed the organizations' cord blood collection inspections. AABB looks at collections and uses the same algorithm for blood collection. It focuses on the role of the CBB and qualifying the supplier.

The groups were then asked how they approach a situation when the outcomes are imperfect (e.g., post transplant, post-thaw CQ data). FACT looks at the information and at how it is collected by banks. Information is variable; some has to come from the transplant center to the bank. FACT standards are very specific on the kinds of information that must be provided.

AABB said that their process is very similar. Because AABB has outcomes data requirements (which vary for products), the banks have to submit them. The expert assessors go on-site and look at the data and ensure that they are being analyzed for tracking and trending. The inspectors know what's in the acceptable range and will comment if this is not met.

The group discussed the FDA guidance around a Basic Licensure Application (BLA) and asked if a facility could not get a BLA, what the impact would be in terms of standards and variances. FACT said that its position was not to have a standard lower than Federal law, although it could have a higher standard. It's possible to have a BLA and not be accredited, for example. AABB had the same response; AABB assesses whether the facility has a BLA.

The group noted that the dilemma of accreditation affects consumer outcomes. Some felt that competition was good and that having only one accrediting body would be less beneficial for patients. Other general comments included the fact that assessing clinical outcomes interacted with the legislation's requirements; thus, it made sense to continue this existing process and not create a new one solely for banks. Some members felt that the ACBSCT should recommend that the CBBs and the accrediting agencies participate in the process, rather than creating a new one. The solution should be adaptable in the future and should also ensure diversity in the program. Models may have to be modified to encourage donation by the minority populations that are hardest to reach.

Some ACBSCT members suggested that the commonalities between AABB and FACT

could be utilized to arrive at specifications. Banks could choose which organization they would seek accreditation from, and then the on-site inspections could be conducted by teams representing both organizations. Members continued to have questions about what, if any, the significant differences there are between the two organizations. It was suggested that they could be asked to define the differences for the ACBSCT members. The broader question would be, given the differences, whether any science lay behind the varying auditing methodologies that would point to preference for one method over the other to identify important factors that affect quality.

HRSA staff felt that the group was on track on the accreditation issue and that there was no expectation that it would solve the issue during the April meeting.

Scientific Registry for Transplant Recipients (SRTR) Presentation on Outcomes Data

- *Greg Levine, SRTR Senior Project Manager, Arbor Research Collaborative for Health*
- *Dr. James Burdick, HRSA, DOT*

SRTR Presentation on Outcomes Data -- Greg Levine, SRTR Senior Project Manager, Arbor Research Collaborative for Health

Mr. Levine said that the Scientific Registry of Transplant Recipients (SRTR) has had the contract for seven years with HRSA and described the SRTR's roles, responsibilities, and its complementary relationship with the OPTN. He reviewed the common statistical methods SRTR uses, including survival analysis and transplant benefit, and the ways in which these outcomes are assessed. A key question is how changes in policies affect these outcomes.

Mr. Levine described the data flow and the provision of data back to OPTN regarding inconsistencies to be followed-up upon. SRTR also conducts program- and/or center-specific reporting; different reports help answer varying questions appropriate for different audiences (e.g., family/patient, payers, transplant centers). There are three types of content for these reports, including detailed tables (on transplant center activities, patient characteristics, and patients' outcomes); and interpretation of statistics. Program-specific reports are updated every six months (January and July), but there are actually six periods throughout the year when data are available (i.e., the July report data are available to the centers in April).

Mr. Levine described how models are reviewed and updated as new data elements become available. He discussed how centers get flagged for review if their expected outcomes are not met.

OPTN Data Collection -- Dr. James Burdick, DOT

Dr. Burdick described the process for collecting data through OPTN, rules for compliance, data audits, and the timelines for providing data. The OPTN final Rule was issued in 2000 and includes non-voluntary data reporting requirements. These are

Federal regulation and enforceable. A few years ago, the community examined the data being collected and reduced the data requirements by 25-50 percent in order to lessen burden and increase the data's usefulness. Dr. Burdick described the possible changes to the data audits that are currently under consideration.

Discussion

The group discussed the importance of trends, and noted that, with stem cell transplantation, the data do not flow the same way as in solid organs.

Need for Public Funding for Required Data Documentation -- Work Group Presentation & Council Discussion -- Karl G. Blume, M.D., ACBSCT Chair

Dr. Blume led the presentation in the absence of the work group chair, Dr. Appelbaum, and Dr. Doug Rizzo also contributed to the presentations. Dr. Blume announced that the work group did not have a written proposal at this time. The data collection requirements can be burdensome and at a very large center can require as many as of 3 FTEs to fill out the data forms. Some transplant centers are working with CIBMTR to estimate their costs for providing the required data. Dr. Rizzo noted that the meetings have been very positive, and he expected good response rates.

Discussion

The group discussed the AGNIS system and linkages with it. Once the linkages are set, data flow into CIBMTR. CIBMTR obtained feedback from many stakeholders on key data elements and used the feedback to create the required data forms. About half of the required data elements are objective (lab data), and the other half require a more subjective review of clinical status. Maintenance should be relatively easy once the system is set up at each center,

A handout included with the meeting materials described costs for various types of centers to link into AGNIS in various ways. A survey of centers indicated that one-third uses a commercially available system; one-third has proprietary systems; and the remaining one-third is less prepared to link with AGNIS. (About half of the 129 centers surveyed responded.) CIBMTR will be looking at where the centers are and their needs in terms of database structure and programmers. Centers for which AGNIS is not viable would use FormsNet (the electronic data capture system) and they would receive tools to get data back for some limited reporting. For the most part, these are smaller centers with lower volume, for which the costs of adopting a new system are prohibitive.

By August 2008, the costs and FTEs should be more clearly defined for the centers using AGNIS.

CMS & Private Insurer Reimbursement for Stem Cell Transplantation

- *Roy B. Jones, Ph.D., M.D., Professor of Medicine and Transplant Physician, MD Anderson Cancer Center*
- *Marcel E. Salive, M.D., MPH, Director, Division of Medical and Surgical*

Services, OCSQ/Coverage and Analysis Group, Centers for Medicare and Medicaid Services (CMS)

Insurance Coverage for Transplant Clinical Trials -- Roy B. Jones, Ph.D., M.D., Professor of Medicine and Transplant Physician, MD Anderson Cancer Center

Dr. Jones addressed the unintended impediments to research and improved clinical care resulting from the fact that the CMS National Coverage Determinations (NCD) Manual is silent on the many transplant indications that are considered to be standard of care by either transplanters and/or commercial insurers. These indications include myelodysplastic syndrome, myeloproliferative disorders, and allotransplants for lymphoma. The decision about reimbursement for these indications is left to local discretion, and local contractors/financial intermediaries (FIs) routinely exclude coverage in the absence of an affirmative NCD.

Dr. Jones described the pros and cons of current CMS coverage, as well as the problems surrounding clinical trials coverage in the absence of an NCD. He suggested that CMS should clarify the clinical trials policy, and it should specify that this clinical trials policy governs where no NCD exists. CMS should also clarify that the clinical trials policy was intended to cover trials designed to define or compare therapeutic activity. NCDs are needed for allotransplantation for Lymphoma, Hodgkin's, Myelodysplastic syndrome, Myeloproliferative disorders, Myeloma (noncoverage); autotransplantation for tandem transplant for myeloma (noncoverage); and Lymphoma.

Dr. Jones noted that there are commercial insurer problems as well, as many increasingly refuse to pay for Phase 2 and 3 clinical trials. Ironically, they will pay for the exact same treatment if it is performed outside a clinical trial. It seems that these payers use a "flag" to deny experimental treatment (e.g. as indicated by participation in a clinical trial), citing CMS' lack of coverage as justification. Clarifying that the Medicare Clinical Trials Policy covers any indication for which there is not an NCD would be extremely helpful.

Dr. Jones summarized the request that CMS update the NCDs to reflect available studies and standard practice (lymphoma, myeloma tandem, MDS, MPD) and to clarify the clinical trial's policy to indicate that it includes therapeutic activity studies of any type and supports studies where the NCD is silent.

CMS Coverage for Stem Cell Transplantation -- Marcel E. Salive, M.D., MPH, Director, Division of Medical and Surgical Services, OCSQ/Coverage and Analysis Group

Dr. Salive commended Dr. Jones and concurred that, within the Medicare program, 90 percent of coverage decisions were made at the local level. He outlined steps to CMS coverage and commented that CMS has no control over some coverage issues, such as benefit categories determined by Congress.

Several things have to happen before CMS considers an NCD. First, the new item or service must fit into an existing Medicare benefit category (which is determined by Congress, not CMS). If the proposed coverage involves a drug or device subject to FDA

approval, it must have received approval for at least one indication. FDA approval does not, however, lead to *automatic* coverage by Medicare; lack of FDA approval for off-label indications should not prevent Medicare coverage, either.

Second, CMS must go a step further and consider if the drug or device is "reasonable and necessary" for the Medicare population (or a subpopulation) – this is often not considered in clinical trials. Dr. Salive described how CMS applies the statue using "reasonable and necessary" requirements: it must have a sufficient level of confidence that the evidence is adequate to conclude that the item or service improves health outcomes, and that it is generalizable to the Medicare population. Evidence about this question is assessed using standard principles of evidence-based medicine.

Dr. Salive described the NCD process and noted instances in which the six-month timeframe could become a nine-month time frame (such as by commissioning an external technology assessment). Diagnostic coverage requires the provision of adequate evidence that the incremental information obtained by new diagnostic technology changes physician recommendations and results in changes in therapy that lead to better patient-centered outcomes among Medicare beneficiaries. Coverage with evidence development is used for promising innovations with insufficient evidence for the Medicare population.

Dr. Salive added that he would be happy to talk with anyone about NCD topics that should be changed or reviewed. The stem cell policy was last revised in 2005 and has been revised four or five time in the last 10 years. CMS is open to revising it again. Dr. Salive described coverage of allogeneic and autologous stem cell transplantation for various indications, and he noted that local coverage policies can be appealed. If there is no policy, there are also ways to appeal a local coverage decision. For clinical trials to succeed, CMS needs to leave a lot of discretion to the FIs.

Discussion

Dr. Parkman expressed the view that coverage should come down from HRSA or CMS; he felt that the science was clear and that there was not much regional variation. California has a precedent that works very well in this area, in terms of clarifying what is and is not covered. He stated that local autonomy does a disservice to the patient and the doctor, although maybe not to the government (the payer).

Dr. Lubin suggested that the group consider genetic diseases as well as malignant ones (e.g., sickle cell) because questions remain around the treatment and it seemed that transplantation might help cure the disease – to everyone's benefit. On myelodysplastic syndrome (MDS), Dr. Lubin expressed horror that patients were put in a position where they had to progress to having leukemia before they could be transplanted – it made no sense because these patients' outcomes are worsened, yet they get transplanted. It is unfortunate that CMS does not pay for MDS transplants, but commercial carriers do. Dr Jones said that, for MDS patients over age 65, the secondary coverage pays for the needed transplant.

Dr. Blume asked Dr. Salive what the chances were of getting these changes made, and if

something like the California model could be reviewed or assessed by CMS. Dr. Salive responded that CMS can open decisions for an NCD upon request from an outside party, or it can open them unilaterally. When CMS hears about things like this from experts, it generally does examine the issue and assess whether it should open a request. CMS also is required to open a request that comes in with evidence; in fact, not only is CMS required to do so, it is ready to do so. Dr. Salive said that no one had formally asked CMS to evaluate the lack of coverage for MDS.

The determination would be based on evidence-based reviews, such as the article mentioned by Dr. Jones. Dr. Salive clarified that Compendia status does not affect coverage for allogeneic transplantation, only for chemotherapy coverage. CMS needed to see the evidence and review it – that was how coverage gets changed. The evidence-based review by ASBMT will be published in August. It would be appropriate, at that point, to officially ask CMS for an NCD.

The group proposed placing this issue on the agenda for the ACBSCT's November meeting.

Program Confidentiality Policies for Cord Blood Donors -- Michelle Bishop, PhD, Work Group Chair

Dr. Bishop announced that the work group met by conference call three or four times and had made progress. She described why confidentiality is critical. The problem at hand was that PL 109-129 specified information that cannot be disclosed about bone marrow donors but did not detail confidentiality provisions for CBU donors. Specific recommendations were needed in this area.

This work group has gathered source materials and has consulted with experts in this area. The work group presented a draft recommendation for the ACBSCT's consideration. There were two main sets of recommendations related to the disclosure of information to cord blood recipients and donor, and to the linkage between the cord blood donor and the donated unit. These recommendations address information that:

- Should *routinely* be disclosed to recipients;
- Should *not routinely* be disclosed to recipients;
- Should *never* be disclosed to recipient (consensus was not reached on all of these); and
- Should *never* be disclosed to the donor.

There were two additional recommendations, as well: that donation is an act of altruism (IOM language), and that consent forms should clearly state that donation terminates a donor's ability to direct the use of cells. The work group felt that the recommendations should apply to both public and private cord blood banks, and that a confidential link maintained by the bank between the donor and the cord blood unit is recommended for safety and for the donor family's well-being.

Discussion

The group clarified that the mother makes the donation on behalf of the infant (some families never tell the baby that he or she donated). Committee members expressed the belief that it was unrealistic to track the donor/baby after 18 years, given how hard short-term follow up is.

The group discussed the feasibility of a nationwide system for tracking/recording cord blood units; right now. The FACT representative clarified that there is a nation-wide and international system, called ISBT that many facilities are moving towards. This system applies to all cellular therapy products.

The group reviewed each recommendation and commented on each one (below):

> ***Recommendation 1:* Information related to the cord blood unit that routinely should be disclosed to patients.** The following information is considered appropriate to disclose to the patient, as it does not present a risk of disclosure of identity of the cord blood donor: Year the cord blood unit was collected; the sex of the donor; the blood group and Rh antigens (ABO/Rh type); the total nucleated cell (TNC) count of the cord blood unit; and the Human Leukocyte Antigen (HLA) level and location of match/mismatch of the cord blood unit. Recipients should be informed and counseled about positive risk-related responses on the maternal health history questionnaire, positive infectious disease marker (IDM) test results, and hemoglobinopathy traits (if known).

The group deleted "newborn anomaly" from the last sentence of this recommendation as in that case the unit would not be used.

> ***Recommendation 2:* Information related to the cord blood unit that is not recommended for disclosure to patients.** The following information should not be disclosed to patients: the allele level of HLA typing of the cord blood unit; the country of origin of the cord blood unit; the name of the CBB; and the unique identification number of the CBB.

The work group added "the name of the CBB and the unique identification number of the CBB" to this recommendation, moving it from Recommendation 3 (information that should never be provided to the patients).

> ***Recommendation 3:* Information related to the cord blood unit that must never be disclosed to patients.** The following information must not be disclosed to patients: the day and month the cord blood unit was collected; the name of the cord blood bank that released the cord blood unit; the unique identification number of the cord blood bank; and, the race/ethnicity of the cord blood donor. The identity of the donor must never be revealed to the recipient. Recipients wishing to show gratitude to their donors should be encouraged to write a general letter of thanks to the National Marrow Donor Program, the Health Resources Service Administration, or other appropriate organization, which could then publicly post the letter on a website or in printed materials.

The work group did not reach consensus on the name of the CBB and the unique identification number of the CBB in its initial discussions. Some members felt that the unit labeling might include this information as a matter of course and wondered how to prevent disclosure if patients saw the label. The ACBSCT members discussed the issues of safety vs. confidentiality and determined that reasonable measures should suffice. The unit's integrity and safety were the most important issues, and it is necessary to maintain the ability to trace a unit back for safety's sake. It was deemed to be unacceptable to jeopardize the unit and the patient's outcome. Families can get a lot of information by accessing the medical records that contain a variety of data.

The group determined not to place things into this "never to be disclosed" category that would be infeasible or complicate the situation for the transplant center or CBB.

> ***Recommendation 4:* Information related to the cord blood unit that must never be disclosed to donors.** The following information must never be disclosed to the donor: the status of donated cord blood unit; that is, whether the unit was discarded, collected, banked, used for research, or used for transplant. In addition, the recipient's identity must never be revealed to the donor.

The group members discussed past experiences in which this information needed to be shared, and they described the potential of telling donors that the unit was not in the bank. There may be scientifically valid reasons to share the information. Follow-up also indicates to donors that their units were placed in the bank and/or have been used.

> **Recommendation 5:** ***A link between the identity of the donor and the cord blood unit is recommended.*** In order for information to be exchanged between the donor family and the cord blood bank regarding test results from the cord blood unit, as well as information about the continued health status donor, a link is needed between the donor's identity/contact information and the cord blood bank.
>
> **A.** Specific permission for maintaining demographic medical information should be obtained from the donor, and the potential risks of breaches of confidentiality should be disclosed.
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> **B.** The donor family should be informed if abnormal conditions are detected in the cord blood when tested. Medical information should be transmitted to the donor's physician, so that the donor family can be appropriately informed. The cord blood bank should attempt to notify the donor family to contact the physician for interpretation of test results.
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> **C.** The donor family should be asked to report any major changes in the health status of the donor. Procedures for how the donor family should contact the bank need to be made clear. Donor families should be given materials that make it easy for them to contact the cord blood bank (e.g., follow-up post cards, cards with telephone numbers and addresses, etc.).
>
> **D.** There are no limits as to how frequently or how long a donor family can be contacted.
>
> **E.** Records must be retained until the cord blood unit is used or discarded.
>
> **F.** All communications and records must be stored in such a way as to ensure

the strictest confidentiality. Records must be protected from accidental or unauthorized access, destruction, or modification through the use of physical security methods (e.g., consent forms, data forms, and servers must stored in locked cabinets or in rooms to which only a small set of authorized employees have access), data encryption and use of passwords, and network security through the use of firewalls and other security methods.

Recommendation 6: ***Cord Blood Donors Must Understand the Limitations of their Rights.*** As stated in the Institute of Medicine report, *Cord Blood: Establishing a National Hematopoietic Stem Cell Bank Program* (2005, p. 118) "those who collect cord blood for public banks should disclose to potential donors all possible clinical and research uses of the cord blood, and furthermore, that donation will terminate a prospective donor's ability to direct the use of the cells."

The group noted that donors may want to retrieve their units, and their ability to do so is likely to be IRB-dependent. Some centers tell donors they can withdraw consent at any time and can get their units back. Other centers' legal counsel has indicated that donors have 30 days to withdraw, and if a donor rescinds consent, the unit is to be discarded rather than returned to the family.

Recommendation 7: ***Policies for Private and Public Cord Blood Banks.*** It is recommended that private cord blood banks follow the above public cord blood bank policy recommendations.

Some group members felt that the recommendations might not be relevant for all private and public banks.

The work group members agreed to continue working on contentious issues and were encouraged to recruit advice and expertise from other members of the Advisory Council. They will report back to the group in November 2008. Dr. Blume congratulated the members for making such good progress.

FDA Update on Cord Blood – Good Guidance Practices -- Ellen Lazarus, M.D., Division of Human Tissues, Office of Cellular, Tissue and Gene Therapy, CBER/FDA

Dr. Lazarus presented an overview of FDA good guidance practices (GGP) and guidance documents. Guidance (unlike a Rule) represents the agency's current thinking on a topic but is not binding. She described guidance development and the specific cord blood guidance for minimally manipulated, unrelated, allogeneic, placental/umbilical units. She provided background and the timeline for this guidance's development.
Discussion

Dr. Lazarus answered a question about the 21 CFR Part 1271 import provisions and the Compliance Program Guidance Manual addendum on imported HCT/Ps, which do not directly apply to unrelated donor HPCs (351 HCT/Ps), by clarifying that her point was to show the FDA's approach. The FDA does not have a Compliance Program Guidance

Manual addendum specific for 351 cord blood. As evident from these import provisions and Compliance Program addendum, the FDA works with the district to facilitate entry of certain HCT/Ps, including HPCs.

Public Comment

None noted.

Tuesday, April 29, 2008

Dr. Blume said that the FDA presentation on regulations (April 28th, 2008) was important for the ACBSCT work. Dr. Kurtzberg would discuss the implications for foreign grafts since she had proposed that the ACBSCT should offer a recommendation to the FDA on this matter.

Dr. Kurtzberg stated that there is nothing about cord blood that indicates it should be restricted to certain uses and suggested the following recommendations be made by the ACBSCT to the Secretary on the issue of cord blood licensure:

- Finalize guidance for licensure;
- Expand scope of clinical indications;
- Define reasonable guidelines for comparability;
- Define rules and processes for use of non-U.S. cord blood units (CBUs) that will not impede clinical practice; and
- Define rules for the transition period when some banks are licensed and some are not.

Dr. Kurtzberg stated that the current draft of cord blood guidance provides a path to licensure only for treatment of patients with hematological malignancies. Additional indications are warranted and have been in clinical practice for 20 years. Cord blood should be licensed for the same clinical indications that are in practice for bone marrow.

The ACBSCT members discussed whether addressing this disease-by-disease made any sense, given what the group heard yesterday. There are two issues at hand: access and insurance coverage. Some group members wondered why it had taken the FDA 10 years to finalize the guidance.

Dr. Ruth Solomon, from the FDA's Division of Human Tissues (CBER), spoke from the audience. She emphasized that the FDA understood all of the issues raised in the discussion and illustrated in the PowerPoint. The FDA cannot provide a timeline and asserted that finalization involves resolution of issues that have been identified during the comment period. The finalization process is ongoing and considered high priority, and the FDA has heard the Council's concerns. She clarified that the indications will be based on scientific indications submitted to the docket. Mr. McGinnis added clarification, which addressed the group's concerns. Dr. Solomon asked the ACBSCT members to submit additional and/or alternative language to the docket and commented that the docket never really closes.

The group discussed the feasibility of getting an IND with the FDA; there were comments about whether the FDA was accepting IND for cord blood banks. Dr. Solomon stated that, when the IND moratorium ends, cord blood banks need to have a BLA or IND submitted to FDA.

The members discussed the recommendations and whether it was appropriate to recommend that the Secretary direct the FDA to finalize the guidance on licensure. The recommendation was maintained. A motion was made to submit the above recommendations to the Secretary; it was seconded and carried unanimously.

Process for Access of Cord Blood Units for Research -- Work Group Presentation and Council Discussion -- Robertson Parkman, M.D., Work Group Chair

The work group had been formed to investigate whether there was any shortage of CBU for research. It was determined that 1,500 units had been made available for research and there appeared to be no unfulfilled requests. Frozen units are also available for research. Therefore, the group determined that there currently is no unmet need for either fresh or frozen units for research. The work group suggested that HRSA set up a section on its existing website containing the HRSA CBB and NHLBI information in order to facilitate contact by researchers who might wish to request units for research. The work group determined that the issue might need to be revisited in a few years to ensure that everything is still going well.

A motion was made to disband the work group; it was seconded and the motion was unanimously approved.

Scientific Factors Necessary to Define a Cord Blood Unit as High Quality -- Work Group Presentation and Council Discussion -- Joanne Kurtzberg, M.D., Work Group Chair

Dr. Kurtzberg noted that there was a handout in the members' packet that summarized this presentation. The charge to the work group was to consider what defines a high quality CBU, whether a high-quality unit is synonymous with a reimbursable unit, and how HRSA's interim requirements for reimbursable CBUs reconciled with a definition of a high-quality CBU.

Dr. Kurtzberg provided HRSA's interim definition and described the various tests used to characterize CBUs. One issue is that the timing of testing varies and is not under a bank's control. Also, a transplant center may not use a trained laboratory to thaw a CBU and therefore risks compromising it. There are also various methods used to process CBUs, which Dr. Kurtzberg described. There are no data to support a specific decision on how to ensure that a unit is high-quality. Studies show that it is very difficult for banks to be consistent in obtaining CD34 or CFU measures for the units. Moreover, according to a recent NMDP study, banks are actually getting worse at this process.

CFU seems to be highly correlated with engraftment. Using an overall multivariate analysis, post-thaw CFU was the best predictor of engraftment and seemed to be better way to look at potency. There are inherent problems in the process, however, including that the recipient is not identified at the time of banking; the time of storage is not known; the post-thaw recovery is not known; and any effects of shipping and storage at the transplant center are unknown. Additional factors include the fact that experience and

performance of the transplant centers' labs in thawing the unit vary. The degree of characterization of CBUs placed in inventory over the past decade was not standardized (only TNC is consistently available on all units); and processing and testing methods have changed over time. Proficiency exercises have failed to demonstrate evidence that multiple banks can standardize CD34 or CFU testing.

Other issues noted include infectious disease exclusions; problems in cell recovery among certain minority donors (primarily African Americans); and, problems with accurately describing donor race/ethnicity.

In conclusion, Dr. Kurtzberg stated that the work group believed that there are laboratory parameters of CBU content that will better predict potency, as compared to TNC, but that these tests need to be defined and validated. These tests may need to be performed on an attached segment to the unit, after a defined time in storage or before release to a transplant center.

Remaining questions include: what is the best test or combination of tests to predict CBU potency; whether the tests can be measured on an attached segment and, if so, whether they will correlate with recoveries from the unit; and whether tests can be identified that correlate with post-thaw CFU (which may be a good test but is hard to standardize and has a 16-day readout).

The work group recommended that two analyses be conducted and noted that the end-product may be an algorithm rather than a parameter. Specifically, the work group recommended that retrospective data be examined to attempt to correlate dosing of TNC, CD34, CFUs and other newer identifiable parameters with clinical outcomes. And, a prospective, laboratory-based study should be initiated by a group of banks to study correlations between TNC, CD34, CFU, and other relevant assays, to determine whether valid, clinically-relevant correlations can be established. Dr. Kurtzberg closed by describing various scenarios that might result.

Discussion

The work group expected to have a recommendation, depending on the support received for the studies, within 6-12 months. The group discussed the fact that banks change the measurements they use over time. Dr. Blume summarized by noting that there are a lot of data, but no clear direction on a recommendation. Dr. Kurtzberg clarified that the work group was going to conduct a retrospective analysis looking at parameters it defined and pull information from both NMDP and other sources to explore the existing data for correlations.

The work group was instructed to continue working on the project and to report back at the November meeting.

Post-Transplant Results: Bone Marrow, Peripheral Blood Stem Cell and Cord Blood Grafts -- Mary Horowitz, M.D., Chief Scientific Director, CIBMTR

Funding for CIBMTR Data Collection Processes

Dr. Horowitz opened by describing the facts in this area. The existing CIBMTR database is made possible by longstanding NIH support. Analysis of this comprehensive dataset informed the choice of key data elements to be mandated by the SCTOD that were used for optimizing analytic methods. A one-time NIH contract allowed the development of AGNIS, and the SCTOD RFP precluded funding transplant centers for the costs of providing data. Yet, the new legislation increased, by three-fold, the number of patients for whom data reporting was mandatory.

The following assumptions governed the development of the SCTOD reporting system: NIH's U24 funding would remain available to collect comprehensive data on a large sample of transplant recipients; comprehensive data would allow periodic reassessment of the variables to be included in the SCTOD database; U24 funds would partially offset the data collection costs, and that some U24 funds would be redirected to help centers connect to AGNIS; some U24 funds would be redirected to collect quality of life (QOL) data; and, research using the comprehensive dataset would complement research using the more limited SCTOD dataset.

The recently announced decrease in funding for the NCI portion of the U24 grant is substantial and is approximately $500,000 per year. This shortfall will affect SCTOD and will prevent expansion of the QOL study. The effect will be that funds to support links to AGNIS will not be available; reimbursement levels for data collection forms will remain static or decrease; and centers will have to meet increased reporting demands of the SCTOD with a shrinking pot of money. If centers elect to provide only the limited SCTOD dataset, the stipulation for mandatory data reporting may result in fewer -- rather than more -- data being available for analysis.

Dr. Horowitz concluded by stating that the SCTOD is not an isolated part of transplantation. There is a need for a broad research agenda that will answer important questions. To this end, AGNIS is important and, therefore, CIBMTR asked the ACBSCT to recommend to the Secretary that NIH restore full funding for the U24 grant.

Discussion

Federal staff noted that it is always possible to submit a request for supplemental funding for U24. Clarification was provided that the 20 percent reduction in funding was for only the NCI portion of the grant. CIBMTR was advised to seek outside funding for data collection activities and Dr. Horowitz noted that the organization does seek (and obtain) such funding, but the shortfall is still $500,000 annually.

The group determined that there was high interest in recommending funding for the data collection processes. A written recommendation was distributed to the group:

The Advisory Council is concerned that reduced funding for Center for International Blood and Marrow Transplant Research (CIBMTR) by the National Cancer Institute

(NCI) will have a substantial, adverse effect on the availability of data and overall state of clinical hematopoietic cell transplantation (bone marrow, peripheral blood, and cord blood) research. Additionally, the Advisory Council is concerned that funding limitations will preclude full implementation of a project for electronically sharing clinical transplantation data using the NCI's caBIG infrastructure (the AGNIS project). The AGNIS project has the potential to greatly facilitate the ability of centers to share data on transplant strategies and outcomes electronically and, by doing so, to increase the scope of clinical research possible in this field in a cost effective manner.

> The Advisory Council specifically recommends that the Secretary of Health and Human Services increase funding of the CIBMTR's U24 cooperative agreement with NCI (U24CA76518) during years two through five to levels at least equal to that requested by CIBMTR and recommended by the NIH's Scientific Review Committee.

Dr. Chell noted that the dollar amount is less important than its timing at the implementation of both AGNIS and the QOL research. Mr. Aronoff stated that the recommendation's introductory statement could note this fact.

Outcomes of Unrelated Donor Transplantation: Are We Making Progress?

Dr. Horowitz stated that, in terms of hematopoietic stem cell transplantation, the survival results are not as good as one would like them to be. Disease status has an impact on early mortality, but it's generally higher with an unrelated donor. For unrelated transplantation, those with an 8/8 HLA match do the best.

The PART (Program Assessment Rating Tool) analysis done during the PART review process indicates that, among the populations studied, there have been significantly improved results in unrelated transplantation over time. This improvement results partly from the fact that better-matched donors are available and selected today. Other factors include better patient selection, less delay in transplant (e.g. patients have fewer prior therapies), better conditioning regimens, better GVHD prophylaxis, and alternative graft sources. It remains a question, however, if the improvements are being seen in all types of transplants, given the fact that the study only included myeloablative transplants.

In terms of the impact of graft source, the trend showed a slight advantage for peripheral blood, mainly among those who had advanced disease. Bone marrow vs. peripheral blood, in early stage of disease, showed no benefit for one compared to the other. In addition, it's important to remember that early outcomes are not everything – studies are needed to look at long-term follow-up to assess therapies' varying impacts.

She summarized by noting that bone marrow, peripheral blood, and cord blood are all effective sources of hematopoietic stem cell transplantation. The choice of graft may depend on donor, patient, and disease characteristics, but there is more that is unknown than known at this point. The field must, therefore, be committed to rigorously evaluating the therapies employed, and do so for both short- and long-term effects.

Current data limitations include the fact that most data about donors derive from experience with unrelated donors and randomized trials of peripheral blood vs. bone marrow (patients are primarily young adults, who are in good health, and the follow up is relatively short and often incomplete). In addition, most data about recipients derive from related donor transplants for leukemia and have short follow-up.

Discussion

The group discussed the interesting finding that there appears to be a dissociation in cord blood between GVHD and what seems to be graft vs. leukemia. Dr. Horowitz noted that the ability to pick more closely matched donors in the adult setting appears to have a lot to do with the improvements noted, as has improved understanding of cell dose.

Cord Blood Use -- Current Patterns & Trends -- Juliet N. Barker, MBBS, Attending Physician, Memorial Sloan-Kettering Cancer Center

Ms. Barker stated that there are many views about the suitability of cord blood as an HSC source. The lack of enthusiasm that some feel about it stems from factors, including delayed engraftment; high TRM in early UCBT experience; discomfort with "new technology;" lack of staff resources to embrace UCBT; unwillingness to refer out from the transplant center; a bias in favor of "in house" approaches; a concept that "we invented it" so it must be the best; the belief that published data doesn't apply to "in house" results; selective tolerance of complications with an "in house" approach; and challenges of the UCB search.

Ms. Barker described outcomes seen with varying degrees of match and said that CBU permits greater HLA disparity. Ms. Barker stated that cord blood is a viable alternative to unrelated transplant. Cord blood expands access to transplants for patients who are not of European descent, and especially for those of Asian, African, and Hispanic ancestry. UCB is also available faster than URD HSC. There are no problems with donor availability, thus the time constraints revolve around the patient and the procedure is easy to reschedule. There has been less-than-expected incidence of GVHD and it appears that chronic GVHD may be easier to treat for cord blood.

Ms. Barker described problems in UCB search, including the fact that some international banks do not provide the needed information for the units; and NMDP-facilitated searches creates a middleman which can slow international searches. MDACC's observation of transplant centers suggests that the centers do not know who they are searching and do not know what to ask for. They have problems navigating searches outside the U.S. There is a need for the minimum requirements for a UCB unit to be both standardized and implemented internationally. In addition, there is a need to simplify the UCB search and make searches more transparent.

She described MDACC's findings on the best units, stating that the best units are 6/6s followed by 5/6s $\geq$ 2.5. Limitations are, however, that most adults do not have such units and that some patients with an "optimal unit" will not engraft. She described means to ensure engraftment and assessed if engraftment was better after a double unit transplant.

Ms. Barker discussed factors that may impact unit quality, including poor volume reduction techniques, a hematocrit higher than 40 percent, incorrect freezing rate at onset of fusion, storage above -196^{o}C, and transient warming events.

Discussion

Ms. Barker was asked if double cord was better than single cord, and she responded that this was not definitive yet. The only data on acute GVHD with double vs. single cords come from Minnesota and are retrospective. The data indicate that acute GVHD is worse in double cords, but this has yet to be published. The caveat is that transplant-related mortality is reduced in doubles.

FDA Clarification -- Ellen Lazarus, M.D., Division of Human Tissues, Office of Cellular, Tissue and Gene Therapy, CBER/FDA

Dr. Lazarus returned to speak about questions raised by earlier conversations and by her presentation the day before. Dr. Kurtzberg's presentation at the beginning of the day included bullets on defining rules for when some banks are licensed and others are not. Dr. Lazarus commented that prioritizing the guidance is a high priority for the FDA and that the final guidance implementation will conclude the current period of delayed enforcement of IND and BLA requirements for minimally manipulated, unrelated allogeneic cord blood. Dr. Kurtzberg clarified that banks will have time to comply and will not be expected to have the IND or BLA on the Rule's publication date.

Dr. Kurtzberg's third bullet addressed reasonable guidelines for comparability, and Dr. Lazarus stated that the FDA guidance intends to be flexible with regard to the methods used by the cord blood banks to demonstrate comparability. The guidance provides some examples but is not prescriptive regarding the methods and assays to demonstrate comparability among currently and previously manufactured cord blood. Dr. Kurtzberg clarified that the bullet meant that the FDA should give examples of sterility, cell counts, recovery post thaw, etc., and Dr. Lazarus responded that there were among the measures suggested in the draft guidance.

On the issue of foreign sources, Dr. Lazarus stated that the FDA has no intention of limiting U.S. patients from accessing products outside the U.S, when such cord blood products are needed for their treatment. Where licensing requirements cannot be met, there needs to be another mechanism for legal importation of such products. She could not provide details regarding how FDA intends to address this issue. The FDA has received many comments on this issue.

Dr. Lazarus asked the ACBSCT to look again at bullets #3 and #5 from the recommendation to assure that they do not unintentionally reduce the flexibility of the existing approach.

Recruitment Practices & Considerations for Cord Blood Donors

- *Wendy Chan, Sr. Director of Operation, Collection and Customer Service, StemCyte International Cord Blood Center*

- *Pablo Rubinstein, M.D., Chief Scientist for Cord Blood, Stem Cells, and Tissue, New York Blood Center*
- *Sue Armitage, Assistant Director, MD Anderson Cord Blood Bank*

StemCyte International Cord Blood Center -- Wendy Chan, Sr. Director of Operation, Collection and Customer Service

Ms. Chen shared her experience conducting recruitment in a public cord blood collection site. Success has everything to do with good quality and good quantity, and compliance is the first priority. In Southern California, where she works, Ms. Chen stated that there is less of a problem recruiting among the Hispanic population, and more difficulties recruiting African Americans. To fill the gap, she worked with other locations, including Atlanta. A community's trust of the medical field and the collection team are both important in securing donations.

Ms. Chen commented that, when the hospitals' doctors and nurses collect, they have only a 20 percent success rate, but when StemCyte's trained staff collects at a hospital, they have a 30-40 percent success rate. Another issue is that the IRB approval can take a long time and one must be patient to secure this and establish a collection team. In addition, relationships with labor department nurses are important, and obstetricians must also be involved. Her facility conducts a large amount of training. The most difficult part of the job is monitoring staff performance – the facility has no field supervisor and has nine collection sites.

In conclusion, Ms. Chen stated that there is no easy way to collect; hospitals differ, and some are more complicated than others. Collections have increased in the last few years, however, so she was optimistic.

New York Blood Center -- Pablo Rubinstein, M.D., Chief Scientist for Cord Blood, Stem Cells, and Tissue

Dr. Rubinstein described the New York Blood Center's recruitment practices. He added that mothers are generally fascinated by the fact that cord blood could be used in this way, rather than being thrown away. Mothers are asked to "assent," not "consent," to the extraction from the placenta. He noted that since hospitals have different populations in terms of maternal race and ethnicity, access to multiple hospitals can ensure, on average, appropriate rates of collection.

Discussion

The group discussed the fact CBU donated from donor mothers that identify the baby donor from multiple broad race groups is an issue and needs to be addressed in the future.

MD Anderson Cord Blood Bank -- Sue Armitage, Assistant Director

Ms. Armitage reported that MD Anderson (MDACC) faced issues similar to those described by the other speakers. Relevant factors include those connected with promotion

(awareness among donor mothers, the target population, nurses, and OBs); recruitment (identification of potential maternal donors, securing consent at the right time); and, donor selection.

For promotion, MDACC explores what the best outreach mechanisms and locations are for various target populations. Because it works best when they communicate with the mother before she comes in for delivery, the program conducts education and promotional outreach at churches, health education programs, and other community programs. It's necessary to have an IRB at the various hospitals so that people can make donations if they so desire. MDACC has seen its refusal rates decline as a result of these strategies.

For recruitment, the bank considers the best place to seek consent before the woman presents at the hospital, and conducts outreach at locations that include clinics and obstetricians' practices. It has received IRB approval to go into the community clinics that serve the public hospital, and this outreach has increased consent – in fact, no one has refused donation under those circumstances.

Ms. Armitage noted that different race/ethnicities had different rejection rates and that the facility lost six percent of White mothers on exclusion risk factors alone (mainly because of travel by on the part of Asian and White women to countries with high malaria risks).

Discussion

The discussion addressed the differences between "assent" and "consent." MDACC reported that its IRB does not include the option of "assent;" instead, it requires full consent. Other centers (such as New York's) have more lenient processes; the goal is to not inconvenience the mothers. Some centers conduct mini-consent and generate more donations that way. The group concurred that, once donation is promoted, the demand must be met. It is not reasonable to promote donation and then turn donors away.

A potential agenda item for a future ACBSCT meeting could be to look at different models for consent and for conducting outreach to various communities.

Additional Work Group Discussions & Recommendation Drafting -- ACBSCT Members

Dr. Blume noted that five work groups had been formed in January and summarized their recommendations. Mr. Aronoff described the process after the ACBSCT made a recommendation to the Secretary. Dr. Blume summarized the work group's activities thus far:

1. Access to CBU for Research -- Dr. Parkman's workgroup recommended practical steps HRSA could take on its Web site to facilitate access to CBU for research (and that this workgroup disband for two years pending a change in availability of CBU for research).

2. Confidentiality – Dr. Bishop's group will revise the table to reflect the discussion. The workgroup will discuss the revisions and present them to ACBSCT members before the November meeting. The recommendations will be formally voted on at the November meeting.

3. Public Funding for Reporting – Dr. Appelbaum's group has discussed plans for a draft and final survey, as presented by Mr. Rizzo. The results of the survey will be ready for the November meeting and will be a major agenda item for that meeting.

4. Cord Blood Bank Accreditation – Dr. Read's group will review the materials that AABB and FACT submitted and try to bring a recommended process for recognition to the November meeting.

5. High-Quality Cord Blood Units – Dr. Kurtzberg's group will conduct a retrospective analysis with the existing data. The group will hold a conference call to identify parameters for this analysis and it will look at possible ways to standardize clinically relevant cell counts and/or correlating results. CIBMTR will use existing data to look at the identified parameters.

Discussion

Dr. Burdick clarified the purpose of the definition of a high-quality cord blood unit and the extent to which these units may be considered to be "reimbursable". He stated that DOT did not seek to address insurance reimbursement in this definition. Dr. Parkman worried that clinicians will have to justify the use of a unit that was not a HRSA-defined "high-quality unit", and that insurers would only pay for those units. Dr. Burdick asked for suggestions on what to substitute for this (other than nothing). Dr. Burdick clarified that the number, as it currently exists, will remain active for the time-being.

Mr. Aronoff asked ACBSCT members to submit potential agenda items. Dr. Regan suggested getting an FDA update on licensing, in terms of whether it is necessary, and its impact on business practices. Dr. Read suggested an agenda item on ISBT labeling.

Public Comment

Kathy Loper from the AABB commented that it might be premature to discuss the ISBT 128 efforts. All organizations have agreed on labeling standards (including FACT and AABB) and will require that labels conform to those standards. The U.S. has not agreed on a uniform label, however, and will be meeting to discuss the issue in May and October 2008. The system is being used, she noted, but it is not completely ready for roll-out yet. She recommended that the ACBSCT wait to have a presentation on this system.

The next meeting will be held in mid-November 2008.