FINAL Meeting Summary of the 10th Cell Therapy/FDA Liaison Meeting
October 21, 2010
Bethesda, MD

Host Organization:

Participating organizations: AABB, AATB, AdvaMed, ASBMT, AATB, BIO, CAP, CIRM, FACT, FDA/CBER/OCTGT, ISCT, NHLBI, NMDP, PACT

Attendees were welcomed by the Co-chairs, William Janssen, PhD and Phyllis Warkentin, MD. The meeting was called to order at 12:45pm and Dr. Janssen gave opening remarks (see presentation #1). Dr. Janssen presented a comparison of related and unrelated donor characteristics from an apheresis director's perspective.

UNRELATED ALLOGENEIC PERIPHERAL BLOOD HEMATOPOIETIC PROGENITOR CELLS

An Overview of Unrelated Donor HPC(A) Usage Under the NMDP-held IND

Presentation by Dennis Confer MD, NMDP

Dr. Confer provided an overview of the National Marrow Donor Program (NMDP) and described their role as a contract holder with HRSA. The NMDP is a member of the World Marrow Donor Association, which is composed of 69 registries and over 120 cord blood banks worldwide. Total growth in the NMDP file was discussed including the addition of 500,000 donors last year. Dr. Confer then reviewed unrelated transplant data by fiscal year and cell source as well as numbers of shipped and imported products. He reported that 18 products per day crossed international borders in 2009 (see presentation #2). Dr. Confer then discussed donor lymphocyte infusions (DLI). He described the rationale for importing products which is driven by HLA type and the need for matched products. This is the single most important factor for predicting survival.

Dr. Confer then reviewed outcomes associated with the NMDP BB IND 6821. The NMDP analyzed factors that influence outcomes. A total of 1,178 transplant recipients were included and parameters included recipient, transplant, donor and product related factors. Of product characteristics measured at the apheresis centers, total volume processed, total white blood cell count and total mononuclear cells (to a lesser extent) were significant predictors of engraftment in univariate analysis. Among the product characteristics measured at the transplant centers, total white blood cells, total

mononuclear cells and total CD34+ cells (to a lesser extent) were significant predictors of engraftment. (See presentation#2). In the multivariable analysis, only the volume of donor blood processed remained a significant factor predicting engraftment. No product factors were found to be associated with survival at 100 days.

The session was opened for questions and the first discussion points were around "who" is performing the collection of these products. He responded that the HPC(A) products are often collected by the same collection centers that collect other apheresis products.

Dr. Witten asked if they had looked at engraftment by size of the collection site and whether there was a difference in volume or product quality from centers of a certain size. Dr. Confer responded that no impact on center size had been seen. She then inquired about the view of NMDP on the questions posed regarding who should hold a license. Dr. Confer responded that they would figure out how to manage the regulatory requirements if the network held the license. The cord blood license/nonlicensed model is probably a good example though there are some potential negative consequences. Dr. Confer added that there were several advantages to NMDP holding a license. The organization would be allowed to continue the current system and collection centers would be unburdened from the responsibility. It would also likely eliminate differences in product pricing which could make it difficult to navigate under licensure.

The questions then addressed whether there was a safety benefit. Dr. Confer responded that these products are fairly straightforward to manufacture and the safety issues are primarily associated with the donors. Some of the items needed are beneficial but expensive (calcium infusions, risks of central line placement). When responding to questions about whether it would impact shipping, he said he did not see a problem even in the setting of multiple licenses. The product viability is fairly reliable though the there is some sensitivity to room temperature conditions.

Steve Bauer, FDA staff member then inquired why overall survival was improving in recent years. Dr. Confer explained that HLA matching is now performed using high resolution typing. This is a major factor accounting for improvement. It is also interesting that there is an increase in survival even for advanced stage diseases. Treatment for graft versus host disease has improved as well as anti-infective therapies. Diane Maloney then asked if NMDP had looked at other factors and Dr. Confer replied, "yes." A meeting participant asked whether all of the donors were mobilized with filgrastim and Dr. Confer responded that all collections under the NMDP IND were using filgrastim. There are some international products that are not under IND where donors are mobilized with lenograstim. In the NMDP protocol, the filgrastim dose was 9-11ug/kg per day for five days. The target was 10ug/kg rounded to the nearest vial.

The National Marrow Donor Program: Unrelated Donor Experiences

Presentation by John Miller, M.D., Ph.D.

Dr. Miller presented a summary of the NMDP experience with unrelated donors. He described some of the questions that still remain regarding optimal stem cell sources for transplant recipients. The safety profiles vary between bone marrow and mobilized peripheral blood stem cells (PBSC) from the donor's perspective. He summarized the information published in a retrospective review in a 2008 edition of Biology of Blood and Marrow Transplant. (See presentation #3)

Dr. Miller reviewed serious adverse events (SAE) following bone marrow donation. A panel of physicians reviewed the data and concluded that 125/9,345 collections (1.34%) experienced a serious adverse event. There were 116 post donation events related to the act of donating and the details were included in his presentation. For PBSC donors, two thirds underwent a second day of PBSC donation. More recently, most donors undergo large volume apheresis such that there are fewer two day collections now than in past years. More female donors needed a central line than male donors. During mobilization bone pain was the most frequent symptom and the sites of bone pain, severity of pain and pain management response were also reviewed. Regarding the frequency of apheresis-related adverse events, female donors also experienced more than males and a total of 50 SAEs were reviewed plus an additional four serious but not unexpected events.

Dr. Miller then presented long term followup data and noted that cancer is no longer considered an SAE as the incidence reflects that in the general population. He then presented a summary of donor symptoms following donation, clarifying that related donor symptoms may be different. He then discussed a current study through CIBMTR looking at related donor safety (RDSafe). The purpose will be to compare the incidence of serious and several adverse events for donors age 18-40 and 41-60 versus unrelated donors. Serious and severe events in donors <18 and >60 will also be evaluated. The trial includes a health-related qualify of life study for unrelated donors and related adult and pediatric donors as well.

As the discussion opened, Dr. Witten asked about the criteria for product type selection. Dr. Miller explained that the transplant physician makes a request regarding the product preference. A donor may have clinical or personal reasons to prefer one method of donation over the other and in those cases, NMDP communicates with the transplant center to determine if they would accept another product type. Some donors are at high risk for anesthesia or have back issues that make marrow donation less desirable and some have personal reasons such as not wanting to take the growth factors. Regarding the question of how standardized the bone marrow donation procedure is today, Dr. Miller responded that it is primarily done for pediatric patients and the numbers of bone marrow products collected have decreased. This makes it difficult to maintain competency and described as an example, the variation of volume of each marrow "pull" during the collection procedure. Phyllis Warkentin added that apheresis collection processess also vary among collection centers. Donna Przepiorka asked if there was an

NMDP quality plan for apheresis centers. Dr. Miller affirmed this is a requirement and shared an example where calcium and central line catheter usage were reviewed, resulting in additional collection center training and subsequent decreased utilization.

The Effects of Filgrastim Mobilization Therapy on Unrelated PBSC Donors – not captured in the PBSC trial

Presentation by Corina Gonzalez, MD

Dr. Gonzalez shared the Georgetown University hospital experience of performing approximately 100 PBSC collections per year, on donors who come primarily from outside of the geographical area. She discussed her experience relating to the physical, psychological and financial impact on unrelated donors. Physical effects are generally resolved and result in a downgrading of adverse events. Most are managed in the urgent care setting and not personalized for each donor. Regarding the psychological effects, many donors, particularly military personnel may have underlying conditions such anxiety, depression and post traumatic stress disorder. These conditions may be exacerbated or symptoms triggered by certain aspects of the donation such as needle sticks, bright lights, or placement in a subordinate position of receiving orders. She shared some details specific to combat experienced donors and added that no withdrawals had been experienced at their center. The financial considerations were then presented. Dr. Gonzalez explained that the time commitment is often more than providers think or expect. Some work half a day if possible but most require time off from work for initial evaluations, injection days, the collection procedure and travel time to and from the collection center. Not all time off is compensated by employers and other mechanisms may be used for compensation (sick leave, vacation time and NMDP reimbursement for unpaid workers). There are often other out of pocket expenses such as child and pet care, meals and transportation.

When the discussion opened, Dr. Gonzalez described that their center has served 5/6 NMDP districts including Puerto Rico. She felt their large volume came from the facilities infrastructure in place such as administrative support, dedicated operating room time and staff and a general sense of prioritization for rapid donor turnaround time. (See presentation #4).

Dr. Janssen asked about whether NMDP had begun looking at the administration and utility of Plerixafor and Dr. Confer responded that the data was limited and there was little donor enthusiasm in the unrelated setting for testing the drug. He added that the recipient would also need to consent and the agent was expensive. The NMDP looks forward to seeing data on its usage as it is published. Dr. Szczepiorkowski mentioned the Dendreon model for a licensed product which uses a contract provider for the raw material. He inquired how FDA would resolve this potential difference in regulation. Keith Wonnacott (FDA) responded that they saw this product as a raw material product collected for further manufacture according to the biologics license application that was submitted. Dr. Wonnacott then asked about the drivers for product selection and asked whether cost would be a consideration. Drs. Miller and Confer relayed the potential

increase in chronic graft versus host disease for PBSC recipients, which also results in an increase in the desirable graft versus leukemia affect. Clinician choices are driven by some data but a large factor is clinical judgment based on the patient disease and treatment plan. Dr. Warkentin added that cost is not a real factor for consideration. Dr. Wonnacott then asked about the CD34+ cell dose and its correlation with outcomes and the degree to which this is under the control of the collection process. He asked what testing is performed at collection and how is product quality controlled. Dr. Confer responded that not all apheresis centers have access to rapid CD34 analysis. Some centers do not receive results back until the evening and others do not receive the results until the following day. The testing methods and results may vary. Overall, most centers rely on their own results when given a choice and the final CD34+ cell dosing level decision is made at the transplant center. Dr. Bauer asked whether a group or consortium had looked at this and was given the response that several attempts had been made to standardize the testing.

Dr. Wonnacott then inquired about the current role of accreditation in the collection process. Dr. Miller explained that there were requirements for a center to participate within NMDP and that the role of WMDA (World Donor Marrow Association) was to serve as the accreditation program for registries. Kathy Loper added that both AABB and FACT standards have requirements in place for a quality plan but the requirements are general and not product specific. A standard might have requirements for personnel, training and equipment management and operation but not specify the specific parameters used to collect a product. Dr. Wonnacott followed by asking about lots that might fail to be transplanted and why this would happen. Dr. Confer explained that this was a very rare event, usually owing to a change in recipient condition. The last question asked about the processes in place for positive sterilities and the speakers explained that the microbial contamination rate is measured as part of process control within most facilities and NMDP but that these products are generally used regardless and before the results are available.

The co-chairs closed the meeting with an invitation to stakeholders and FDA to offer suggestions for the next Cellular Therapy FDA Liaison meeting.