CIBMTR®
CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

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# contents



## CIBMTR Working Committees in the Spotlight

We continue our series focusing on the work of the Working Committees of the CIBMTR. The Working Committees provide scientific oversight for the use of CIBMTR data and statistical resources.

Their responsibilities include designing and conducting studies relevant to their subject area and involving CIBMTR data, statistical resources, networks and/or centers; considering proposals to use CIBMTR data for studies pertinent to their subject area; periodically assessing and revising relevant sections of CIBMTR data collection forms; planning and conducting workshops at CIBMTR meetings.

Working Committees have responsibility for setting priorities for observational studies using CIBMTR's large clinical databases. These observational studies are a core activity of the CIBMTR. For a full listing of the 19 Working Committees and their leadership, point your browser to http://www.cibmtr.org/COMMITTEES/Working_Committees/index.html.

In this issue, we highlight the work of the Late Effects and Graft Sources and Manipulation Working Committees.

## The Late Effects Working Committee

The Late Effects Working Committee (LEWC) conducts clinical research on late effects following hematopoietic stem cell transplantation. We take advantage of the large clinical database of the CIBMTR to study long-term effects of transplant, ranging from second-malignancies to quality-of-life studies. With the increasing number of transplants being performed and better supportive care, there are more and more long-term survivors and our mission is to understand their late effects.

The LEWC is headed by 3 co-chairs: Brian Bolwell, MD (Cleveland Clinic Foundation), John Wingard, MD (University of Florida) and David Jacobsohn, MD (Children's Memorial Hospital). The chairs are assisted by the Scientific Directors J. Douglas Rizzo, MD, MS and Navneet S. Majhail, MD, MS and statisticians Kathleen Sobocinski, MS and Jerry (Zhiwei) Wang, MS, Ruta Bajorunaite, PhD and John P. Klein, PhD.

The LEWC promotes and develops the scientific agenda, establishes priorities, and ensures the progress of the research studies and publications. The committee meets yearly at the BMT Tandem Meetings and the co-chairs meet monthly by teleconference with the CIBMTR staff.

This year, our committee has identified 3 target areas of post-transplant late-effects that deserve specific attention: fertility, liver toxicity, and quality-of-life after transplant. Subcommittees have been formed and are meeting by conference calls. The goals are

>> Continued on Page 5

## CIBMTR Graft Sources and Manipulation Working Committee

The Graft Sources and Manipulation Working Committee (GSMWC) addresses scientific questions related to graft procurement, quality, and manipulation and is one of the most active and prolific committee's of the CIBMTR. This committee has collaborated with other registries, national and international, and the resulting publications have led to practice changes with respect to graft choices when considering HLA-matched sibling and unrelated donor transplantations for leukemia.

The Statistical Center and the committee would like to acknowledge the leadership and scientific contributions of Dr. John Wagner who served as committee co-chair for over a decade. The committee is now chaired by Adrian Gee, PhD (Baylor College of Medicine), Richard E. Champlin, MD (M.D. Anderson Cancer Research Center), and Mary J. Laughlin, MD (Case Western Reserve University). The chairs are assisted by the Scientific Director, Mary Eapen, MD, MS and statisticians Fangyu Kan, MS, MA and Mei-Jie Zhang, PhD.

Our committee membership is comprised of investigators of diverse backgrounds and experience in clinical transplantation and cell processing and manipulation, providing the opportunity for synergy in scientific interactions, stem cell technology development, and new ideas. Our committee is a lively and interactive group that

>> Continued on Page 5

## CIBMTR Newsletter Survey

***Please take a few minutes to participate in our brief survey about the CIBMTR Newsletter. Thank you!***

***Find it online at:***

http://www.surveymonkey.com/s.aspx?sm=YbVOIMVbHcmNYmTqlGtv_2bw_3d_3d

# Update on the Stem Cell Therapeutics Outcomes Database (SCTOD)

*by J. Douglas Rizzo, MD, MS*

Two years have passed since the CIBMTR received the contract to collect data for all allogeneic hematopoietic cell transplants (HCT) in the United States (US) as part of the C.W. Bill Young Cell Transplantation Program. Although much work remains, considerable progress has been made in bringing this program to fruition.

## Data Collection

Virtually all transplant centers in the US, and a large majority of those who collaborate with the CIBMTR internationally are now aware of the changes brought by the SCTOD. US and international centers continue to complete and submit new (or updated) Data Transmission Agreements (DTA) that provide for the exchange of data (and payment for data) between centers and the CIBMTR. Centers with outstanding DTAs are encouraged to complete these documents. Reimbursement for Report Forms submitted to CIBMTR is conditional upon receipt of a completed DTA. Similarly, the new observational database research protocol and consent documents covering submission of data to the CIBMTR are in their second year, and a majority of US centers have completed the necessary steps to gain approval of these important documents from local IRBs. Consent for use of data for research should be sought from every patient for whom data will be sent to the CIBMTR, regardless of whether the data is submitted on a TED level or comprehensive Report Form level.

New TED level and comprehensive Report Forms released in December of 2007 are generally working well for data collection. Questions regarding these forms suggest thoughtful consideration by data professionals at the centers, and several of these questions will lead to changes in the forms with the next iteration. CIBMTR does not intend to make large-scale changes to any of the data collection forms over the course of the next year, to allow sufficient time for electronic and other systems to reach stability. Small changes that affect form completion logic will happen intermittently.

## FormsNet™

Along with the release of new data collection instruments, CIBMTR has also launched the FormsNet™ application to capture data electronically. As of this writing, all US HCT centers have the ability to access FormsNet™, along with the majority of international centers. Almost 200 centers are using FormsNet™ to enter at least some of their data, and more than 60,000 individual forms have been processed by FormsNet™ since inception. This represents a considerable shift in data submission for most HCT centers, a trend which we anticipate will continue over the next few years with increasing adoption of electronic data submission. CIBMTR staff also use this application for data entry, and provide important feedback about the application.

As with the launch of any major software application, there has been considerable turbulence in the first 9 months of the FormsNet™ life cycle. Information services staff on both the Milwaukee and Minneapolis campus have been devoted to resolving issues with the application. Issues addressed include improvements in the error message and error correction screens, enhanced search features in the centers' forms due screen, improvements in system stability, and various bug fixes. Perhaps the largest system repair currently in process involves the forms due listing. The complexities of bringing together two separate databases and data systems into a consolidated work list involving more than 260,000 patient records led to several problems with creation of forms due lists for each transplant center. CIBMTR has been in the process of implementing the repairs, with progressive improvement visible to FormsNet™ users since July 2008. To accommodate the needs of centers to have an accurate Forms Due listing, the Continuous Process Improvement (CPI) program has been placed on hold until the forms due reports can be issued. Teams are still expected to complete the appropriate forms for related and unrelated HCT recipients, but formal CPI reports are suspended. Once the forms due repairs are complete, CPI expectations will be resumed. Information about the FormsNet™ application is regularly communicated with users via email, as well as a Google User "Tip of the Week" and Google User Group. These communication tools augment the direct communication with CIBMTR staff dedicated to each center, as well as postings of frequently asked questions on the CIBMTR website.

Several enhancements to FormsNet™ are planned over the coming months, some in response to user requests. These will include features to improve the work processes of data personnel such as: improved patient and center forms due screens which can be sorted, filtered and exported to Excel; tools for team liaisons that will allow them to assist centers with forms and data corrections; and general enhancements to improve stability and add functionality. Additionally, for HCT programs outside the US who wish to provide comprehensive data to the CIBMTR, functionality to accept pre-TED data from the EBMT via a dataset provided from ProMISe and generate a request for comprehensive Report Forms is in process. Likewise, centers who wish to provide data to CIBMTR for all patients at their center to establish a complete dataset, regardless of provision of consent for research, will be able to accomplish this in the coming months. An agreement will be needed between the interested centers and CIBMTR before this can be put into effect.

## AGNIS - Messaging System

Work continues on the AGNIS system to better facilitate electronic data exchange between centers and the CIBMTR. Data elements are being "curated" with the NCI's cancer data standards repository (caDSR) such that all data exchanged will comply with a national data standard. CIBMTR staff actively collaborate with staff from the NCI team to increase the efficiency of the process. Curation occurs on a form by form basis, and as of the time of this writing, the 2400, 2450, 2004, 2005 forms are fully defined, with several of the Report Forms in process. Data has been exchanged for some of these forms using the AGNIS messaging system in collaboration with the AGNIS user group. Parties interested in learning more about AGNIS, or joining the AGNIS user group are encouraged to visit www.agnis.net. In addition to StemSoft, several other software development companies have expressed interest in learning more about AGNIS, and may begin to develop applications for the HCT environment. Potential users making queries of software vendors are encouraged to learn more about the vendor's intentions to use AGNIS in their product. As AGNIS becomes more robust, CIBMTR will be creating a web-based seminar series to provide further specific information to potential transplant and IT users, as well as considering subsequent in-person meetings in a format similar to the IT Summit held in Minneapolis in January 2008.

Systems used to collect data on behalf of the HRSA are required to pass a rigorous security audit conducted by the HRSA Office of Information Technology. After a year of preparation, CIBMTR completed an extensive System Test and Evaluation in June of 2008, and anticipates full certification and authorization before the end of 2008. Similar status is already held by NMDP, and should bolster confidence that protected health information submitted to CIBMTR systems is indeed held under secure conditions.

## Center Specific Outcomes

The new Program requires that CIBMTR conduct analyses of HCT outcomes on a center by center basis and make such reports available to the public. CIBMTR is committed to conducting an equitable center-specific

analysis report with scientific rigor to fulfill these requirements for allogeneic HCT recipients in the United States. To achieve this, we have been working with the ASBMT Quality Outcomes committee to be certain current data collection instruments collect data relevant to this task. Recently, a forum was held in Milwaukee in September to discuss and develop a plan to conduct these analyses. A group of nearly 50 people representing the HCT community, solid organ transplant experts (who conduct similar analyses annually), experts from other medical communities conducting and reporting hospital outcomes, payors, government agencies, and patients attended the 2 day meeting. A report will be generated and circulated to Transplant Center directors before the 2009 BMT Tandem Meetings, and the plan will be presented at the Medical Directors conference during the 2009 BMT Tandem Meetings.

CIBMTR anticipates that 2009 will be a year of ongoing improvement in the functionality of the systems supporting the SCTOD. We appreciate the patience of HCT centers, banks, and other entities interacting with the CIBMTR as the complex program is being implemented. ■

## Perspectives

*by Stella M. Davies, MBBS, PhD, MRCP*

*Chair, CIBMTR Advisory Committee,*
*Professor of Pediatrics, Cincinnati Children's Hospital Medical Center*

### Funding the CIBMTR

The large CIBMTR database and the outstanding and unique research that comes from it is an expensive proposition. Funding the registry is like painting a bridge; as soon as you are done for one year it is time to start again for the next year. Over the years, funding has come from a U24 grant from the US government, competitive grant applications from a range of agencies and foundations, and from fundraising efforts, bringing in donations from family foundations, industry partners and individuals. Recently the NIH announced that funding would be cut across the board to all grant recipients; which meant a cut of half a million dollars a year for the CIBMTR. CIBMTR reached for the phones, and with active lobbying by a number of parties, the CIBMTR funds slated to be cut had been restored. This was excellent news, but reminded us all that funds from any source - National Institutes of Health, competitive grants or philanthropic funds - can never be taken for granted. Everyone in the CIBMTR community should remain alert for funding opportunities - grants we can apply for specific research studies, opportunities for philanthropic giving and personal donations. We will need to continue to paint the bridge for many years to come!

### National Marrow Donor Program

The US National Marrow Donor Program (NMDP), a close partner of CIBMTR, has been operating for 20 years. During this time NMDP has achieved a number of extraordinary goals, including the growth of the registry to over seven million registered potential volunteer donors. The recruitment and HLA-typing of such a large group of individuals has lead to enormous improvements in HLA-typing techniques with molecular methods of typing now in general use, offering greatly improved allele discrimination compared with older serological techniques. The high volume of typing required by NMDP has pushed laboratories to make typing assays more rapid and less costly, and in the near future it is hoped that the majority of new donors recruited to the registry will have molecular typing at HLA-A,B,C and DRB1. The NMDP's achievements of the first 20 years are detailed in a very encouraging supplement to the journal "Biology of Blood and Marrow Transplantation". Survival rates in children after transplantation from an unrelated donor have doubled during the period of operation of NMDP, with similar improvements in adults - an extraordinary achievement. Interestingly, most of the improvement in survival has come in the last 5-8 years, during which time high resolution typing of donor and recipient has become required, HLA-C has been added to the match algorithm, and the registry size has increased markedly. I believe all of these improvements have enabled more children to be transplanted with well-matched donors in 2008, and this is supported by retrospective high resolution typing of donor-recipient pairs transplanted throughout the lifetime of the NMDP. These data show that only 21% of children transplanted between 1987 and 1995 were well-matched (as we now define it: 8 alleles, HLA A,B,C and DRB1) with their donor, compared with 52% of those transplanted between 2003 and 2006. These improvements, together with improvements in supportive care (i.e. viral surveillance and treatment, anti-fungal prophylaxis) mean that outcomes of children receiving well-matched unrelated donor grafts are now truly comparable to outcomes of sibling donor transplants. This is leading to re-evaluation of the indications for transplantation. If a sibling donor transplant is considered, transplant from a well-matched unrelated donor should be as attractive an option for the child with no sibling donor. These findings may also reduce the need for complex and expensive strategies such as pre-implantation genetic diagnosis to obtain a sibling donor for children likely to need transplant at a future time. It is gratifying to see so much progress in what I consider to be a short period of time. We have much to look forward to as operation of registries in the US and elsewhere continue to improve. ■

## 2009 BMT Tandem Meetings

*The combined annual meetings of the Center for Blood and Marrow Transplant Research (CIBMTR) and the American Society for Blood and Marrow Transplantation (ASBMT) are North America's largest international gathering of blood and marrow transplant clinicians and investigators, laboratory technicians, transplant nurses, pharmacists and clinical research associates, since 1995.*

**REGISTER TODAY!** for the 2009 BMT Tandem Meetings which will be held February 11-15 at the Tampa Convention Center in Tampa, Florida. Scientific Program Chairs for 2009 are Drs. Mark Litzow representing CIBMTR and James Ferrara for ASBMT.

Detailed information about the 2009 BMT Tandem Meetings will be continuously updated on the CIBMTR (www.cibmtr.org) or ASBMT (www.asbmt.org) web sites, including online conference registration and hotel reservations. Check back periodically for updates to the provisional agenda.

In addition to five days of scientific and clinical meetings, related peripheral meetings will include: BMT CTN Steering Committee, BMT CTN Coordinator and Investigator Sessions, FACT Training Workshops, Clinical Research Professionals' Data Management Conference, BMT Center Administrative Directors Conference, BMT Pharmacists Conference, Transplant Nurses Conference and BMT Center Medical Directors Conference. Watch the web sites for updates regarding dates and times for peripheral conferences. Sessions targeted primarily to pediatric cancer will be held on Thursday, February 12. ■

# The Blood and Marrow Transplant Clinical Trials Network

## History

The Blood and Marrow Transplant Clinical Trials Network (BMT CTN), established in October 2001 as a National Institutes of Health (NIH)-funded initiative to conduct large, multi-institutional clinical trials addressing important questions in hematopoietic stem cell transplantation (HCT), was first described in the CIBMTR Newsletter in January 2003. By then, the fundamental infrastructure had been set in place and the first 2 protocols were under development. Since 2003, the Network has evolved into a dynamic and successful enterprise focused on improving survival for patients undergoing HCT. Over 2400 patients have been enrolled on 15 protocols during the past 5 years.

The primary goal of the BMT CTN is to provide answers to critical questions in current HCT medical practice that can change practice and improve patient outcomes. To achieve this goal, the Network emphasizes trials that require resources beyond the capability of any single institution. The large databases and statistical capabilities of the CIBMTR greatly enhance the Network's ability to design and plan trials and are an invaluable asset for the activities of the BMT CTN.

## Organizational Structure


Figure I. BMT CTN Organizational Structure

The BMT CTN is a multifaceted organization (see Figure 1) that is comprised of several interactive components including:

- The original 16 Core Clinical Centers (some of which are consortia of two or more centers) each with a cooperative agreement from NHLBI and NCI to participate in the Network
- 80 Affiliate (previously known as non-Core) Centers contributing ~25% of the total number of patients accrued to Network trials
- A Steering Committee which is responsible for the selection, design, execution and analysis of all Network studies
- Administrative and Technical Committees which are responsible for addressing specific areas of Network activity
- Study-specific protocol teams which develop, implement and monitor BMT CTN trials and participate in data review
- Ad-hoc committees which address specific issues such as the development of protocol concepts in particular subject areas
- The Data and Coordinating Center (DCC) which is a consortium of 3 organizations and the base unit supporting all Network activities: The Center for International Blood and Marrow Transplant Research (CIBMTR), National Marrow Donor Program (NMDP) and the EMMES Corporation (see Figure 2). The DCC is responsible for maintaining the continuity of operations and effective communication, data management and statistical support activities.

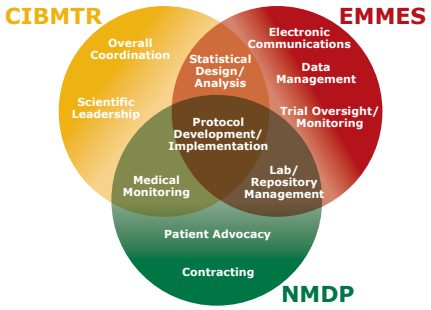


Figure 2 BMT CTN DCC Relationship Model

Each organization and committee brings both shared and unique skills that are vital to the overall success of the Network.

## Protocol Activity

Since activation of the first trial in late 2003, three protocols have completed planned accrual. Currently there are 12 open protocols actively accruing patients. Two more protocols will open soon and 3 new protocol concepts were presented to the BMT CTN Steering Committee in July 2008 and approved for further development. For more information on the completed and ongoing protocols, visit the BMT CTN public website at www.bmtctn.net.

Not only is it important to prioritize, select, design and implement protocols wisely, but timely enrollment of patients to open protocols is critical. Research answers are needed while the question is still relevant. Since initiation of the Network, attention has been focused on establishing good working relationships with Affiliate Centers and with the NCI-funded Cooperative Groups that perform clinical trials for diseases for which HCT may be a treatment consideration. In recent years, collaboration with these groups has resulted in enhanced accrual both to BMT CTN-led trials and to several trials led by the Cooperative Groups. Representatives from the Southwest Oncology Group (SWOG), Cancer and Leukemia Group B (CALGB), Eastern Cooperative Oncology Group (ECOG) and Children's Oncology Group (COG) have all collaborated with the BMT CTN in disease-specific protocol development as well as in the approval of NIH guidelines addressing logistical issues of working together. All agree that there is benefit to working together early in protocol development to avoid duplication of scientific research efforts. In the process:

- The enrollment of the NCI credit system has been preserved
- A collaborative per-patient payment system has been established
- Network trials have been opened through the NCI Clinical Trials Support Unit (CTSU)
- A mechanism has been established for an expedited review by a single scientific review committee, either the NHLBI-appointed Protocol Review Committee (PRC) or Clinical Trials Evaluation Program (CTEP).

Through its early experiences, the BMT CTN has learned much about the potential barriers to accrual to BMT Trials and now considers these in the very earliest concept discussions. A full-time Accrual Specialist focuses on developing protocol-specific plans to proactively address accrual for each trial from design through completion.

## Research Agenda

Prior to the initiation of the Network, a State of the Science Symposium was convened in collaboration with the American Society for Blood and Marrow Transplantation (ASBMT) and the NIH. Six key areas were identified as high need for clinical investigations and became the blueprint for trial prioritization. These are:

- Expanding and evaluating alternative donor and graft sources;
- Reducing regimen related toxicity;
- Improving graft versus host disease (GVHD) prevention and therapy;
- Decreasing risks of recurrent malignancy post transplant;
- Decreasing post transplant infections and enhancing immune recovery;
- Prevention and treatment of late effects and improving quality of life after HCT

The BMT CTN Steering Committee added a seventh focus area; evaluating and improving the outcome of HCT for rare diseases. All of the noted areas have been addressed as the primary or secondary specific aims of one or more trials.

In June 2007, a second BMT State of the Science Symposium was held to determine the future research agenda of the Network. Advance work prior to this Symposium resulted in the development of 12 Working Committees which brought together scientific leaders, domestic and international, from the fields of HCT, oncology, hematology, immunology and biostatistics to determine the most critical issues in HCT still requiring investigation. This forum generated eleven protocols rated by the BMT CTN Steering Committee as high priority (6 of which were rated as "very high priority"). A summary of

these proceedings was published and can be found at: Biol Blood Marrow Transplant. 2007 Nov;13(11):1268-85.

## Future Activity

Several of the trials already completed or close to completion have set the stage for follow-up studies requiring resources beyond the next several years. As it looks to the future, and building on past accomplishments, the BMT CTN, now in its 8th year, is actively involved in the process of securing approval from the Institutes for renewal in 2011. The Network continues to look forward to successful completion of clinical trials, activating new studies in collaboration with other cooperative groups performing clinical trials and maturing the portfolio shaped by recommendations of experts in the transplant community.

The article on CLINT (Facilitating International Prospective Clinical Trials in Stem Cell Transplantation) in this Newsletter reports a long time relationship with the CIBMTR. Some CLINT members also participated in the 2007 BMT State of the Science Symposium sponsored by this Network. Due to accrual issues noted above, the BMT CTN has already turned to international centers (Canadian and German blood banks as well as Hôpital St. Louis, in Paris, France) for support and collaboration in the completion of two of its trials. This has not been without challenges but the Network remains optimistic that working relationships with transplant centers across the Atlantic will prove valuable to both endeavors. The BMT CTN congratulates the EBMT for its progress on the CLINT Project and looks forward to trans-Atlantic collaboration.

If you are interested in more information about the BMT CTN or any of its activities, please visit its public web site at www.bmtctn.net. ■

*CIBMTR Graft Sources and Manipulation Working Committee*
*Continued from Page 1*

influences clinical patterns through the publication of important clinical study results. The committee meets in-person annually at the BMT Tandem Meetings.

The committee has 14 on-going projects which are listed below. The success of the committee is dependent on scientific interactions, new ideas and active participation of junior and senior investigators. Please contact one of the Chairs or the Scientific Director to learn about the committee or to discuss ideas and new projects.

## Recent publications:

**HC98-05** Outcomes of transplantation of unrelated donor umbilical cord blood and bone marrow in children with acute leukemia: a comparison study. Eapen M, Rubinstein P, Zhang MJ, Stevens C, Kurtzberg J, Scaradavaou A, Loberiza FR, Champlin RE, Klein JP, Horowitz MM, Wagner JE. Lancet 369:1947-1954, 2007.

**D00-65** Peripheral blood grafts from unrelated donors are associated with increased acute and chronic graft-versus-host disease without improved survival. Eapen M, Logan B, Confer D, Haagenson M, Wagner JE, Weisdorf, Wingard JR, Rowley S, Stroncek D, Leitman S, Gee A, Horowitz MM, Anasetti C. Biol Blood Marrow Transplant 13:1461-1468, 2007.

## Studies in progress:

**HC03-01** Prevalence of microbially contaminated hematopoietic stem cell products and its impact on hematopoietic recovery and early survival. (PI Dr. Champlin)

**R02-42** Quantization of the cellular composition of bone marrow and peripheral blood progenitor cells and its effect on outcomes after unrelated donor transplantation. (PI Drs. Collins and Wiesdorf)

**GS05-01** Outcomes after cord blood transplants: examining processing methods. (PI Dr. Chow)

**GS05-02** Comparison of outcomes after transplantation of G-CSF mobilized bone marrow versus non-mobilized bone marrow grafts or peripheral blood grafts from HLA-matched sibling donors for patients with severe aplastic anemia. (PI Dr. Chu)

**GS06-01A** Donor characteristics as risk factors in recipients after transplantation of bone marrow or peripheral blood from HLA-identical sibling donors. (PI Dr. Passweg)

**GS06-01B** Donor characteristics as risk factors in recipients after transplantation of bone marrow or peripheral blood from unrelated donors. (PI Dr. Passweg)

**GS06-02** The role of HLA-C matching on hematopoietic recovery and survival after umbilical cord blood transplantation. (PI Drs. Eapen and Rocha)

**GS07-01** Reduced intensity transplant conditioning regimen: relative efficacy of peripheral blood progenitor cells and bone marrow. (PI Dr. Champlin)

**GS07-03** Unrelated donor transplantation for pediatric acute leukemia: relative efficacy of peripheral blood progenitor cells and bone marrow. (PI Dr. Ringden)

**GS08-01** Impact donor age on outcomes after unrelated donor bone marrow or peripheral blood progenitor cells. (PI Dr. Kollman)

**GS08-02** Are transplant-outcomes inferior (or superior) if an elderly matched sibling is the donor of choice compared to a matched adult unrelated donor for older patients with hematological malignancies? (PI Drs. Alousi and Champlin)

**GS08-03** To determine the clinical benefit, if any, of in-vivo T-cell depletion of grafts from adult unrelated donors with reduced intensity transplant conditioning regimens. (PI Drs. Ho and Soiffer)

**GS08-04** Are two-year leukemia-free survival rates comparable after unrelated donor (bone marrow or peripheral blood progenitor cells) and mismatched cord blood (single unit) transplants in adults with acute leukemia? (PI Dr. Wagner)

**GS08-05** Higher total nucleated cell dose and CD34+ content improves hematopoietic recovery and survival after unrelated donor cord blood: examine the role of single versus double umbilical cord blood transplantations. (PI Dr. Sphall) ■

*The Late Effects Working Committee*
*Continued from Page 1*

to determine whether the current database adequately meets our needs to collect information that address these issues. If not, the subcommittees will recommend specific questionnaires to be incorporated into the CIBMTR forms. Furthermore, the subcommittees may plan publications based on what is learned regarding these late effects with the current database.

## Recent publications:

**LE99-01** The Late Effects of Cancer and Hematopoietic Cell Transplantation on Spouses/Partners Compared to HCT Survivors and Survivor-Matched Controls. Bishop MM, Beaumont JL, Hahn EA, Cella D, Andrykowski MA, Brady MJ, Horowitz MM, Sobocinski KA, Rizzo JD, Wingard JR. J Clin Oncol 25:1403-1411, 2007. b.

**LE05-02**: Bone Marrow Contributes to Epithelial Cancers in Mice and Humans as Developmental Mimicry. Cogle CR, Theise ND, Fu DT, Ucar D, Lee S, Guthrie SM, Lonergan J, Rybka W, Krause DS, Scott EW. Stem Cells 25:1881-1887, 2007

## Studies in progress:

**LE98-05** Solid Cancers after allogeneic hematopoietic cell transplantation. (Study Chairs: J. Douglas Rizzo, Rochelle E. Curtis, H. Joachim Deeg, Gérard Socié, John R.Wingard. Study Statistician: Kathleen A. Sobocinski).

**LE98-07a** Risk of early versus late lymphoproliferative malignancies after allogeneic hematopoietic cell transplantation (Study Chairs: J. Douglas Rizzo, Rochelle E. Curtis, H. Joachim Deeg, Gérard Socié, John R.Wingard. Study Statistician: Kathleen A. Sobocinski).

**LE99-01** Quality of Life and Relationships after Blood and Marrow Transplantation (Study Chairs: Michelle Bishop, John Wingard).

**LE00-02** Late outcomes of auto-transplants for Leukemia/ Lymphoma. (Study Chairs: J. Douglas Rizzo, Hillard Lazarus, and Navneet Majhail).

**LE06-01** Single nucleotide polymorphism analysis in patients who developed AML or MDS after auto SCT for Lymphoma (Study Chair: Timothy Fenske).

**LE07-01** Second malignancies and late effects in patients treated with hematopoietic cell transplantation using reduced intensity conditioning regimens (Study Chairs: Olle Ringden, Navneet Majhail, Jonas Mattsson).

**LE07-02** Duration cGvHD and late effects in HCT survivors (Study Chair: Navneet Majhail).

**LE07-03** Long-term survival and late deaths after allogeneic hematopoietic cell transplantation (Study Chairs: John Wingard, Gerard Socie, Brian Bolwell).

**LE08-01** Risk of 2nd solid cancers in BuCy hematopoietic cell transplantation (Study Chairs: Navneet Majhail, Ronald Sobecks, John Wingard, Brian Bolwell, Gerard Socie).

We invite all members of CIBMTR to participate in our committee and provide new proposals or get involved by providing input in design and conduct of ongoing studies. Proposals may be submitted throughout the year and are reviewed during our monthly conference calls and at our annual committee meeting during the BMT Tandem Meetings. ■

# CLINT Review

*by Jane Apperley and Fiona McDonald on behalf of the CLINT Project Steering Committee*

The CLINT project is aimed at supporting the European Group for Blood and Marrow Transplantation (EBMT) in developing the infrastructure to conduct trans-European clinical trials and facilitate international prospective clinical trials in HCT.

Together with the EBMT, Imperial College London, the Centre for Professional Ethics at the University of Central Lancashire in the UK and the CIBMTR as an Associated Partner, this two year project is funded by the European Union from April 2007 – March 2009.

The key goals of the CLINT project are to:

- Establish the methodology to support prospective clinical trials in Europe,
- Standardize essential data collection and develop a clinical trials database to enable data sharing for meta-analysis with other national and international transplant organizations,
- Overcome ethical and legal challenges for trans-national HCT research,
- Develop a portal for information exchange on clinical trials in HCT and to link to external databases and systems, including AGNIS,
- Improve bio-statistical methodology for the analysis of HCT data.

CIBMTR plays an important role in the CLINT project through sharing the experience of building a clinical trials infrastructure through BMT CTN and by collaborating in the harmonization of data collection forms, database linking, development of bio-statistical methodology and information sharing; all of which will facilitate international prospective clinical trials in HCT in the future.

## Background and overview of obstacles to academic led clinical trials in Europe:

There is a good history of prospective clinical trials in Europe run through individual transplant centres, national study groups and the EBMT. But in recent years it has become increasingly difficult to run such studies in the academic setting due to the introduction of new legislative, administrative and ethical requirements to satisfy the European Union Directives on Clinical Trials. National differences in the implementation of the Directives have also added to the complexity and cost of running trans-national prospective clinical trials, making the task of 'Sponsor' a particularly onerous one.

## Recognized obstacles in trans-national collaboration in HCT

- Difficulties in implementing the EU Clinical Trials Directive for both academic & multinational studies
- Differences in national resources available for the infrastructure for HCT and clinical trial participation
- Difficulties in exchange of patient derived information and material across national boundaries
- National differences in approaches to the ethics of clinical trial participation and of collection and use of tissue for research
- National differences in establishing informed consent
- Lack of systems to exchange information
- Fragmentation of databases and the information stored therein
- Lack of consensus on statistical methodologies across Europe
- Lack of dissemination of information to all interested parties

The CLINT project sets out to develop the EBMT's clinical trials infrastructure to meet the demands of sponsorship under the EU directive and to overcome other obstacles to pan European studies. It will work toward facilitating international prospective clinical trials in HCT through the development of common data sets, linking of databases, building international consensus on bio-statistical methodology and better information sharing on clinical trials.

## Project overview:

### Establishing the methodology to support prospective clinical trials

The focus over the last 18 months has been on the development and implementation of an internal review process for EBMT sponsored trials. An overview of the process is included on the Clinical Trials section of the CLINT webportal (www.clint.ebmt.org).

A core set of Standard Operating Procedures (SOPs) has also been produced and these are currently being expanded and updated to ensure that the EBMT is able to meet standards required for Registration-level clinical trials' management.

Over the course of the project CIBMTR and EBMT have shared knowledge and experience on methodology for the approval and conduct of prospective clinical trials, including documentation and processes. The input of CIBMTR through their association with the BMT CTN has proved to be very beneficial in this regard.

Ten prospective clinical trials are currently being run under the EBMT umbrella. An overview of all major prospective clinical trials in HCT at the national and international level is to be made available on the CLINT webportal in order to improve information sharing amongst investigators and to inform the public on clinical trials activity in the field.

### Standardizing essential data collection and development of a clinical trials database

Standardization of data collection is an ongoing and long-term project of the EBMT and CIBMTR and this area of the project is being jointly chaired by Mary Horowitz, CIBMTR Chief Scientific Director and Carmen Ruiz, Head of the EBMT Registry.

Standardization is essential for reducing the data reporting budget and labor burden placed on transplant centres and this is a key objective of both organizations. The initial focus of this work was on reviewing the Minimum Essential Data (MEDA/TED) and reaching agreement on a core data set. This was accomplished by June 2007 and the new MED A form was implemented in the EBMT database in January 2008. A number of additional items required by CIBMTR have been included in an appendix to the MED A in order to facilitate reporting by centres who wish to submit data to both EBMT and CIBMTR. The appendix has been implemented in the EBMT database to facilitate the transfer of this data to CIBMTR.

Given the successful progress in this area of the project, it was decided to extend the project deliverables to include comparison and agreement of a core data set for cord blood transplantation. At the end of 2007 Vanderson Rocha went to the CIBMTR for 10 months to harmonize the reporting elements and data flow and the goal is to finalise the data set and produce a common cord blood form. It is also expected to improve data sharing at a broader level by providing a link from AGNIS to the EBMT database and CLINT portal.

In March 2007 the EBMT, in collaboration with the CIBMTR, the Asia Pacific Blood and Marrow Transplant Registry (APBMT) and the World Marrow Donor Association (WMDA), convened a meeting in Lyon to discuss the establishment of a global network of outcome registries called the Worldwide Network for Blood and Marrow Transplantation (WBMT). The WBMT will seek to maintain consensus on a common data set for donors and recipients at a global level. At the 3rd WBMT meeting, held in Florence on 2 April 2008, CIBMTR gave an update on the development of AGNIS and plans for implementing a data pipeline for the sharing of cord blood data between EBMT, CIBMTR and Eurocord. Work is currently ongoing to curate the cord blood and fundamental transplant data elements to enable the linking of systems as soon as this is technically feasible. In the future this will facilitate the sharing of clinical trials data for meta analysis between different trials groups.

### Overcoming ethical and legal challenges for trans-national HCT research

The Centre for Professional Ethics at the University of Central Lancashire in the UK has been working closely with the EBMT to evaluate how to overcome ethical and legal challenges for trans-national HCT research. This includes a series of questionnaires and workshops organized at EBMT annual meetings to evaluate:

- National legislative uptake of the EU Clinical Trials Directive, describing discrepancies in ethical/legal guidelines and regulations that hinder trans-national cooperation in HCT trials,
- Issues arising in relation to Informed Consent and Data Protection in the context of trans-national HCT research.

This work will enable the EBMT to identify key problems, develop methodologies and make policy recommendations which will form the basis of reports to be shared with the EU and national authorities in Europe.

**Developing a portal for information exchange on clinical trials in HCT**

A portal aimed at researchers in the field of HCT is being developed to incorporate clinical trials and statistical information. Information held in different databases will be linked into one data management system that will store relevant data on clinical trials in HCT. The portal will be incorporated within the CLINT project website so that information of relevance can be made available to the general public, with the objective of providing key facts on the progress of science in the field of HCT and ensuring widespread dissemination of project information.

**Improving bio-statistical methodology for the analysis of HHCT data**

Led by Myriam Labopin and Aurelien Latouche at the EBMT Data & Study Office in Paris, a review of existing bio-statistical literature has been completed and a manuscript on end point definitions has been prepared and is being externally reviewed by John Klein, PhD of the Medical College of Wisconsin. There are plans for further methodological papers aimed at providing information and guidance for clinicians. Publications aimed at bio-statisticians are also envisaged under the project and will be made available on the Statistics section of the CLINT portal.

The importance of building relationships between statisticians in Europe and the US in order to reach international consensus is recognized and collaborative work between Myriam Labopin (EBMT), Aurelien Latouche (EBMT), Jason Fine (North Carolina), Jan Beyersmann (Freiburg) and Ruta Bajorunaite (CIBMTR) has already begun. As part of this process, Drs Fine and Beyersmann were invited to participate in a round table discussion at the EBMT 2008 meeting to consider methodological issues relevant to HCT. Regular meetings and collaboration between statisticians will be fostered over the course of the project and a second roundtable discussion is planned at the EBMT 2009 meeting with the participation of Mei-Jie Zhang, PhD from CIBMTR.

Work is underway to create the Information Technology (IT) structure on the CLINT portal for exchange of data and analyses and to incorporate the software. Aurelien Latouche will work with the statistical department at the University of Freiburg on this aspect of the project. Software has also been developed at the University of Leiden to enable interactive visualization of statistical analyses underlying publications. This enables interaction between statisticians and offers a valuable educational tool. This tool will be made available via the CLINT portal and authors will be encouraged to make their statistical analyses widely available in this way.

## The future

The CLINT project lays the foundation for future international collaboration in the field of HCT and will strengthen the potential for essential academic-led clinical trials requiring a trans-national or international focus. This will hasten the evaluation of new treatment strategies and improve the outcome for patients worldwide. For further information on the CLINT project visit: http://portal.ebmt.org/CLINT/Pages/CLINT.aspx or contact: clint@ebmt.org. ■

## RCI BMT—Another Addition to the Alphabet Soup for Clinical Trials in Transplantation!

*Marcie Tomblyn, MD, MS and Rebecca Drexler*

Clinical trials remain the cornerstone for advancing medical care. The spectrum of clinical trials requires the innovation of investigator initiated, single center pilot trials followed by smaller phase II trials before conducting the larger phase II and pivotal phase III clinical trials. In the field of blood and marrow transplantation, many centers perform too few transplants in a single disease to answer even preliminary clinical questions in a timely manner. This leads to delay in conducting the necessary larger trials that move the field forward. Recognizing this, in 2005 the CIBMTR formed the Resource for Clinical Investigation in Blood and Marrow Transplantation (RCI BMT) to provide statistical expertise and data management services for smaller multi-center phase I/II trials.

The goal of the RCI BMT is to bridge the gap between these single-center pilot studies and the larger phase II and phase III studies conducted by the Blood and Marrow Transplant Clinical Trials Network (BMT CTN), also coordinated by the CIBMTR in collaboration with the National Marrow Donor Program and the EMMES Corporation.

The RCI BMT coordinates and manages all aspects of these "bridge" trials, including the identification of up to 10 US CIBMTR centers for participation in a specific study leading to more rapid accrual and, thus answers for our patients. In addition to study coordination and center identification, the RCI BMT provides a medical monitor, data auditing, electronic data capture, and statistical analysis for every trial.

Similar to the observational research conducted by the CIBMTR, we have established a process by which investigators submit study proposals. Using email and a proposal template available on our website, investigators may submit their proposal throughout the year. Proposals are then reviewed by the Clinical Trials Advisory Committee (CTAC). The CTAC provides recommendations for proposals relative to scientific merit, feasibility, and alignment with the CIBMTR scientific agenda. This committee meets at least twice a year, always at the annual BMT Tandem Meetings. Decisions for further development are based on the CTAC recommendations as well as an assessment by the RCI BMT Executive Committee regarding staffing issues and identified financial support for a particular trial.

Since the inception of the RCI BMT, a total of fourteen proposals have been received and reviewed at CTAC meetings of which four were recommended for further development. Protocol teams are created and consist of the protocol chair, a protocol officer who is a CIBMTR scientific director, and a representative from each of the identified participating sites.

Currently, the RCI BMT is facilitating the following trials:

- **05-DCB:** Myeloablative Double Cord HCT for Hematologic Malignancies
- **06-DON:** Related Donor Safety and QOL trial
- **07-REV:** Evaluating the safety and tolerability of maintenance lenalidomide
- **08-AZA:** A study to assess the 1 year progression free survival following 5-azacytadine induction reduced intensity allogeneic HCT in MDS

In addition to management of these trials, the RCI BMT participates in additional activities supporting clinical research in transplantation. Some of these include:

- Supporting the NMDP PBSC clinical trial
- Supporting the CTN 0201 PBSC vs. Marrow trial
- Coordinating unrelated donor sample collection for several studies
- Supporting trial initiation and accrual management of CTN trials
- Supporting an NMDP Office of Patient Advocacy study on the financial impact of transplant on patients and their families

For further information, please refer to our website: http://www.cibmtr.org/SERVICES/Clinical_Trials/. ■

## Our Supporters

Thanks to the many contributors who have joined our international collaboration for research in blood and marrow transplantation. We gratefully acknowledge the support of the Medical College of Wisconsin; the National Marrow Donor Program; the National Cancer Institute; the National Heart, Lung and Blood Institute; the National Institute of Allergy and Infectious Disease; Office of Naval Research; Health Resources and Services Administration (DHHS) and the generosity of the supporters listed below.

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