CIBMTR®
CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

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contents

PERSPECTIVES: CIBMTR REVIEW 2009

by Stella Davies, MBBS, PhD; Chair, CIBMTR Advisory Committee
Cincinnati Children's Hospital, Cincinnati, OH, USA

The ability to grow and change is pivotal to the long-term success of any organization. CIBMTR has grown and changed a great deal over the years of its existence, ensuring that the organization remains vital and relevant. A key driver of this change has been regular external review of the operations of the organization and of the scientific agenda.

A previous review of CIBMTR took place in 2002, and resulted in five major recommendations, all of which have been implemented in full or in part. The 2009 review – looking at both our scientific agenda and our internal processes – took place over the course of several months this summer.

External Scientific Review

The external review panel consisted of the following hardworking individuals, whom we thank for their assistance. They represent a wide range of expertise that impacts on CIBMTR:
Outcomes Research: Richard Champlin, Smita Bhatia, Tom Price, Machi Scaradavou, John Levine, Vanderson Rocha
Immunobiology: Nelson Chao, Anat Tambur, Ned Waller
Clinical Trials: Fred Appelbaum (Panel Co-Chair), David Dilts, Richard Larson, Marty Tallman
Statistics: Craig Beam, Ed Gehan
Health Services Research: Craig Earle, David Howard
Cellular Therapy: Helen Heslop, Armand Keating (Panel Co-chair), Jonathan Serody
International Issues: Carmem Sales-Bonfim, Alejandro Madrigal
Bioethics: Art Derse, Steve Joffe
Patient Advocacy: Denny Lorentz, James Omel
Government Partners: Nancy DiFronzo (NHLBI), Bill Merritt (NCI), Bob Baitty and Jim Bowman (HRSA), and Bob Hartzman (Office of Naval Research).

Prior to the review, each participant received several background documents. They then prepared written critiques that were consolidated and shared prior to meeting in person on Sept. 14, 2009. That all-day session started with an overview of CIBMTR by staff, followed by breakout sessions focusing on specific topics. Recommendations from the review were summarized and then distributed to the panel for review and feedback. The revised summary was presented to the CIBMTR Advisory Committee in November for development of action plans.

We are particularly proud of the strengths that the panel identified about CIBMTR, which included the following characteristics:

- Strong leadership;
- Exceptional theoretical and practical biostatistical expertise;
- High quality longitudinal database;
- Large repository of cells and DNA;
- A focus on outreach to stakeholders in developing policies and processes;
- Facilitation of the mandatory reporting that has resulted from U.S. legislation;
- International collaboration;
- Scientific productivity for observational studies;
- Effective coordination of BMT CTN and successful recruitment to clinical trials;
- New initiatives in Health Services Research and Cellular Therapy;
- Development of young investigators.

The panel also made a series of recommendations for future development and implementation of the scientific agenda. Several criteria were used to prioritize the recommendations made by the panel, to determine what CIBMTR should focus on in the near term and into the future. The criteria included an evaluation of the cost, speed of implementation, probability of success, ownership of the plan, and who would review its progress.

Following are the recommendations that will guide CIBMTR over the next few years:

- Develop a system for examining CIBMTR's overall observational research strategy, to ensure that resources are being used to address the most important issues.

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- Develop a formal process for setting the scientific agenda of the Resource for Clinical Investigation in Blood and Marrow Transplant (RCI BMT).
- Develop strategies to bring observational studies to completion more quickly, including
  - Principal Investigator education;
  - Project Manager support for committees;
  - More MS statistician support.
- Enhance data collection and sharing with centers and cord blood banks.
- Facilitate access to data by use of technology.
- Enhance website to allow patients and investigators to get more relevant information, including "take home" messages from CIBMTR studies.
- Increase use of Repository for immunogenetic and immunobiologic studies.
  - Disseminate information about what is available in the Repository more widely, to reach persons with the necessary expertise to do appropriate studies.
  - Make the process for prioritizing/ adjudicating use of samples more transparent.
  - Seek additional NIH funding for genome-wide association/functional studies.
- Expand the focus for using hematopoietic stem cells in cellular therapy other than hematopoietic reconstitution.
  - Initially focus on cellular therapy in a transplant setting, e.g. donor leukocyte infusion
  - Partner with investigators in cardiovascular area
  - Consider joint meeting.
- Establish a long-term follow-up program that includes collecting information directly from appropriately-consented patients.
- Develop the Health Services Research Program. Convene a conference of experts to separately consider this issue and make recommendations for structure and prioritization – what can CIBMTR uniquely do?

Internal Process Review

The internal review of CIBMTR processes emphasized developing more efficient and effective operations. It included an examination of policies, procedures, staffing and communications, and provided an opportunity to further integrate the teams from our two campuses.

With the aid of an external consultant, the review team from both campuses looked at our processes for forms revision, data management and observational studies.

That group, which generated more than 200 ideas, consolidated them into action items for immediate implementation:

- Six for our forms revision processes, focusing on assessing the impact of forms changes and tracking changes.
- Five for data management processes, focusing on moving data through the system more efficiently, improving internal communication and tracking study queries.
- Ten were in the observational study area, focusing on efficient weekly statistical meetings, as well as uniform data retrievals and other measures to ensure data quality.

Please watch us over the next months and years to see how we improve by implementing these great recommendations. And many thanks to all those who helped CIBMTR become an even better source for improving hematopoietic cell transplantation research! ■

CIBMTR WORKING COMMITTEES

Observational research is at the core of our organization. These studies are conducted under the auspices of 19 scientific Working Committees, which are comprised of basic and clinical scientists with expertise in HCT and related disciplines.

Each Working Committee is responsible for designing and conducting studies relevant to its subject area, considering proposals to use CIBMTR data for pertinent studies, assessing and revising relevant sections of CIBMTR data collection forms, and planning and conducting workshops at CIBMTR meetings.

The Committees are led by co-chairs with not only acknowledged expertise in their subject area, but also demonstrated commitment to the work of CIBMTR. Committees are also staffed by CIBMTR Statistical Center physicians and statisticians who work collaboratively with investigators to design and conduct the studies. The following two articles are installments in our series focusing on the work of individual Working Committees. For more information, please go to http://www.cibmtr.org/COMMITTEES/Working_Committees/index.html.

WORKING COMMITTEE: CELLULAR THERAPY INITIATIVES

by Marcelo C. Pasquini, MD, MS

Novel applications of cellular therapies are currently under study. Among these is the use of cellular therapies to treat post-transplant complications with unmanipulated or genetically modified bone marrow or umbilical cord blood cells. Others use cells with the intent to "regenerate" organ function, or cellular therapy for regenerative medicine.

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DONOR HEALTH AND SAFETY WORKING COMMITTEE

By Steven Goldstein, MD

With its first official meeting taking place at the 2005 BMT Tandem Meetings, the Donor Health and Safety Working Committee (DHSWC) is one of the younger CIBMTR Working Committees. The DHSWC research priority is to understand the impact of donation on both related and unrelated hematopoietic stem cell donors. These goals are pursued through both retrospective and prospective studies.

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CELLULAR THERAPY INITIATIVES

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Strictly speaking, bone marrow regeneration by donor cells has long been the hallmark of hematopoietic cell transplantation (HCT). However, cellular therapy for regenerative medicine indications go beyond the HCT field with applications in cardiovascular, neurologic, autoimmune diseases, and more. In all of these areas, HCT-related cellular therapy and cellular therapy for regenerative medicine are the main topics of study of the Cellular Therapy Working Committee (CTWC).

The objectives of this newly developed committee, led by Armand Keating, MD, Helen Heslop, MD, and Joshua Hare, MD, are to optimize collection of data on donor cellular infusion in the transplant setting, develop a database for cellular therapy for regenerative medicine and oversee the Working Committee's research agenda.

HCT-related donor cellular infusion

Data on donor cellular infusion is routinely collected in the post-Transplant Essential Data (post-TED) registration and follow-up baseline report forms. However, as donor cellular infusion applications have evolved rapidly in the last five years with the utilization of mesenchymal stromal cells for treating graft-versus-host disease, and with extended applications of genetically modified cells for treating and preventing post-transplant complications, the forms must be updated to capture this information.

In addition to collecting data, an important goal of the CTWC will be to study long-term outcomes after a variety of types of donor cellular infusions for different indications.

Transplantation is becoming safer, with lower transplant-related mortality because of reduced conditioning regimen intensities and the use of novel approaches for graft-versus-host disease prophylaxis (such as rigorous T-cell depleted grafts or post-transplant cyclophosphamide infusions). Some of these therapies reduce the need for chronic post-transplant immuno-suppressants; however relapse and infectious complications persist as significant challenges. Using donor cellular infusion as a mechanism for launching new post-transplant therapies to maximize immune reconstitution and immune-mediated graft-versus-malignancy effects could reduce complications and improve transplant outcomes in the future.

Regenerative Medicine

The CTWC initiatives are designed to study uses of tissue-specific progenitor and stem cells for indications other than hematopoietic recovery, reversal of inborn errors of metabolism or treatment of primary immunodeficiencies. CIBMTR will provide the infrastructure to allow long-term follow-up of patients treated on cellular therapy trials.

Cellular therapy is an emerging field, with data still maturing and with uncertainty about which diseases are most likely to benefit. Furthermore, there is little or no integration among the groups of different medical specialties involved.

Data collection will be challenging, since early studies under the U.S. Food and Drug Administration's Investigational New Drug Program may not allow data sharing, and the practice of registering cases is not common outside the HCT field.

Development and implementation of the cellular therapy for regenerative medicine database will be done in stages. Initially, the data will include registration information at a single time point without longitudinal reporting. The timeline of cellular therapy may change depending on the disease indication it is used for, and follow-up forms will be instituted in subsequent phases.

A registration form, the Cellular Therapy Essential Data (CTED), was developed by a task force of CTWC members, and is slated to be launched in 2010. The committee will also be surveying U.S. and Canadian centers on their activity in this area. This survey will help identify centers with active cellular therapy for regenerative medicine clinical trials and yield information on what indications are being studied.

Research Agenda

During the last BMT Tandem CTWC meeting, the committee approved three study proposals:

- **CT 0-9-01:** Follow-up of subjects receiving genetically modified cell products post transplant (PI: Helen Heslop, Armand Keating and Edwin Horwitz).
- **CT 0-9-02:** Annual activity survey of cellular therapy for regenerative medicine (Marcelo Pasquini, Steven Pirog and Helen Baldomero).
- **CT 0-9-03:** Follow-up of subjects receiving ex vivo expanded cord blood and mesenchymal stem cell products (PIs: Elizabeth J. Schpall and Catherine Bollard).

These proposals represent the next steps for the committee. Its members are eager to move this exciting new arena forward, and would welcome the participation of new members. ■

2010 BMT TANDEM MEETINGS

by D'Etta Waldoch Benson, CMP

The combined annual meetings of CIBMTR and 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.

REGISTER TODAY! for the 2010 BMT Tandem Meetings, to be held February 24-28, 2010, at the Rosen Shingle Creek Convention Center in Orlando, Florida. Scientific Program Chairs for 2010 are Jeffrey S. Szer, MD, representing CIBMTR, and Joseph H. Antin, MD, for ASBMT.

In addition to five days of scientific and clinical meetings, the 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, BMT Center Medical Directors Conference, Mid-Level Practitioners Conference and sessions targeted primarily to pediatric cancer practitioners.

Detailed information will be continuously updated on the CIBMTR (www.cibmtr.org) and ASBMT (www.asbmt.org) websites. Online conference registration, hotel reservations and the abstract submission program (abstract deadline was Oct. 15) are all there for your convenience.

For general information, please e-mail D'Etta Waldoch Benson, CMP, at the conference office at Bmttandem@cs.com. Questions regarding support opportunities may be directed to Sherry Fisher at slfisher@mcw.edu or 414-805-0687.

DONOR HEALTH AND SAFETY

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Membership in the DHSWC spans a broad range of clinical and laboratory interests, from adult and pediatric clinicians and stem cell collection centers, to donor advocates. Under the leadership of Co-chairs Michael Pulsipher, David Stroncek, and Susan Leitman; Biostatisticians Brent Logan and Tanya Pedersen; and Scientific Director Dennis Confer, this committee has already established a successful publication track record and an ambitious agenda despite its relatively short tenure.

To date, three papers have been published focusing on donor outcomes and the impact of donor characteristics on transplant outcomes. And an important survey looking at the practice patterns of transplant physicians in evaluating sibling donors has been submitted for publication:

- Pulsipher MA, Chitphakdithai P, Miller JP, Logan BR, King RJ, Rizzo JD, Leitman SF, Anderlini P, Haagenson MD, Kurian S, Klein JP, Horowitz MM, Confer DL. Adverse events among 2408 unrelated donors of peripheral blood stem cells: results of a prospective trial from the National Marrow Donor Program. *Blood* 2009: 113; 3604-3611.
- Pulsipher MA, Chitphakdithai P, Logan BR, Leitman SF, Anderlini P, Klein JP, Horowitz MM, Miller JP, King RJ, Confer DL. Donor, recipient, and transplant characteristics as risk factors after unrelated donor PBSC transplantation: beneficial effects of higher CD34+ cell dose. *Blood* 2009: 114; 2606-2616.
- Miller JP, Perry EH, Price TH, Bolan CD Jr, Karanes C, Boyd TM, Chitphakdithai P, King RJ. Recovery and safety profiles of marrow and PBSC donors: experience of the National Marrow Donor Program. *Biol Blood Marrow Transplant.* 2008 Sep: 14(9 Suppl); 29-36.
- O'Donnell P, Pedersen T, Confer D, Pulsipher MA, et al. Practice patterns for evaluation, consent and care of related donors and recipients at hematopoietic stem cell transplant centers in the United States. *Submitted.*

The DHSWC has several exciting studies in progress, now that data collection forms for donors of both bone marrow and peripheral blood grafts have been standardized. These studies will:

- Provide a comprehensive analysis of the related donor experience (DS05-02 RDSafe: A multi-institutional study of hematopoietic stem cell donor safety and quality of life. PI: M Pulsipher).
- Describe cases of cytogenetic abnormalities arising in the recipient that are of donor origin (PI: N Frey).
- Provide important new information regarding the safety and outcome of alternate collection strategies (PI: S Pincus, in collaboration with the Graft Sources Working Committee).
- Evaluate the impact of second donations on marrow and PBSC donors (PI: D Stroncek).
- Evaluate the effect of race, socioeconomic status and donor center size on donor experience (PI: M Pulsipher).
- Comprehensively analyze and compare acute and chronic donor toxicities associated with bone marrow and peripheral blood stem cell collections from unrelated donors (PI: M Pulsipher).

The CIBMTR Statistical Center and DHSWC would like to especially acknowledge the dedication and leadership of Michael Pulsipher, MD, as the outgoing Committee Co-chair. His efforts have set a high bar of accomplishment that the committee is eager to maintain with the support and enthusiasm of its membership.

The DHSWC encourages participation from the transplant community, and especially new members, in current studies or through the submission of new proposals. As a point of intersection between different groups such as the Graft Sources and Cellular Therapy Working Committees, the DHSWC is a natural direction for the scientific growth of the CIBMTR. The potential for collaboration with peers is exponential and provides an exciting opportunity to bring ideas to fruition. ■

CIBMTR HEALTH SERVICES RESEARCH PROGRAM

by Navneet Majhail, MD, MS

Health services research (HSR) is defined by *Academy Health Reports* as "the multi-disciplinary field of scientific investigation that studies how social factors, financing systems, organizational structures and processes, health technologies, and personal behaviors affect access to health care, the quality and cost of health care, and, ultimately, our health and well-being; its research domains are individuals, families, organizations, institutions, communities, and populations."

Several health policy issues are unique to hematopoietic cell transplantation (HCT), in part because it is a resource-intense and costly procedure. These include disparities and barriers to accessing both HCT and long-term care after HCT; referring physician, transplant provider and center practice variations; infrastructure and capacity for transplantation; economic aspects of HCT; and quality of care after transplant.

Health policy and health services-related research are not new to CIBMTR. Recognizing the need for more information in this area, the CIBMTR Health Policy Working Committee was formed in 2005. Previous CIBMTR health policy studies primarily used our existing database and focused on the effects of age, gender and race upon access and outcomes of HCT. The Health Policy Working Committee recognized that resources and expertise beyond those that the CIBMTR observational database and research program provided were needed to answer other important health policy-related questions – we needed to have a dedicated HSR Program.

In 2009, CIBMTR and the NMDP Office of Patient Advocacy collaborated to initiate a formal HSR Program. Its objective is to develop a well-balanced portfolio of health policy-related research studies to increase access to HCT and improve patient outcomes, including quality of life after transplant.

CIBMTR's extensive experience and expertise in conducting HCT-related research, and its existing database and statistical resources are assets to the development of this program. The Stem Cell Therapeutic Outcomes Database contract, with its mandate that all transplant centers within the United States report outcomes data to the CIBMTR, greatly enhances our ability to conduct important HSR studies.

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CIBMTR HEALTH SERVICES RESEARCH

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The newly-developed HSR Program complements the activities of the Health Policy Working Committee. The committee will continue to be an important avenue for HSR studies that utilize the observational database, and its co-chairs will be a part of the oversight group providing guidance to the HSR program.

Research that requires additional resources will be conducted through the HSR Program. We anticipate that most of these projects will require extramural grant funding. We also plan to partner with investigators from within and outside the HCT community who want to conduct health services research related to transplantation.

Some projects that are now underway through the HSR Program are:

- **Factors affecting participation in sickle cell disease trial:** Focus group studies were conducted to identify and understand barriers to clinical trial participation among African-American children with sickle cell disease, and their parents. Optimal methods to communicate information about sickle cell disease clinical trials to the African-American community were identified.
- **Financial impact study:** A pilot study to determine the feasibility of studying out-of-pocket costs and the long-term financial impact of allogeneic HCT. Results of this three-center pilot will be used to plan a multi-center investigation of financial impact of allogeneic HCT.
- **Caregiver initiative:** The HSR Program and the NMDP Office of Patient Advocacy are partnering with Michelle Bishop, PhD, at the University of Florida, on a pilot project using a toolkit with information and stress-management techniques for caregivers, to improve their quality of life.
- **Rural health initiative:** This study is studying the effectiveness of a 12-week telephone support group for marrow or cord blood transplant survivors who live in rural areas.

As it evolves, the HSR Program will address other important research questions related to HCT and will advance the CIBMTR's mission to be a leader in HCT-related research. ■

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK (BMT CTN)

by Sarah Mull, Program Coordinator

Since opening its first clinical trial in November 2003, the BMT CTN has enrolled more than 3,000 patients on 18 different studies that address important issues in HCT.

Network activity

There are currently eight open protocols actively accruing patients. Three more are anticipated for release by the end of 2009, and five additional protocols are in the development phase. Since January 1, 2009, five protocols have successfully completed accrual. They include:

- **BMT CTN 0201:** Peripheral blood versus bone marrow grafts for unrelated donor transplantation.
- **BMT CTN 0303:** T-cell depleted HLA-identical sibling transplants for acute myelogenous leukemia.
- **BMT CTN 0401:** BEAM vs. Bexxar-BEAM for autologous peripheral blood stem cell transplantation for non-Hodgkin lymphoma.
- **BMT CTN 0703 (SWOG S0410):** Tandem autologous transplantation for Hodgkin disease.
- **BMT CTN 0704 (CALGB 10004):** Maintenance therapy with lenalidomide versus placebo following autologous stem cell transplantation for multiple myeloma.

Publications and presentations

In July 2009, the first manuscript with outcome data from a Network study was published in Blood (BMT CTN 0302: Etanercept, mycophenolate, denileukin, or pentostatin plus corticosteroids for acute graft-versus-host disease: a randomized phase II trial from the Blood and Marrow Transplant Clinical Trials Network). In addition, a manuscript for BMT CTN 0101 (fungal prophylaxis) has been submitted and an abstract for BMT CTN 0303 (AML T-cell depletion) will be presented at the American Society for Hematology meeting in December 2009.

Additional accomplishments

- Close to 200 people attended a Graft-versus-host-disease Workshop co-sponsored by NHLBI, NCI, NIAID, FDA, CIBMTR and ASBMT on May 19, 2009, to consider appropriate study endpoints and designs for evaluating agents and strategies aimed at reducing or treating graft-versus-host disease.
- Revisions to the BMT CTN Manual of Procedures are ongoing. Anticipated completion is December 2009.
- Management of the BMT CTN Repository was successfully transferred to the National Marrow Donor Program Research Repository.

Network Renewal Update

The BMT CTN continues to work with NIH program staff on the activities needed to secure continued funding beyond 2011. CIBMTR faculty made several presentations to NCI regarding the importance and achievements of the BMT CTN. Final NCI approval for issuing a Request for Application to renew the BMT CTN grant is anticipated in fall 2009. A similar review process is just beginning at NHLBI. For more information about the BMT CTN or any of its activities, please visit our re-designed public Web site at www.bmtctn.net. ■

STEM CELL THERAPEUTIC OUTCOMES DATABASE (SCTOD) UPDATE

By Carol Doleysh, BS, CPA, Program Coordinator

In the three years since CIBMTR received the contract to collect data for all allogeneic HCTs in the United States, considerable progress has been made in implementing the SCTOD program.

Much of the work over the past several months has focused on updates to FormsNet™2, the online program for submitting HCT data to CIBMTR. These enhancements improved donor and recipient form functionality and added clinical trials and continuous process improvement (CPI) functions.

AGNIS (A Growable Network Information System)

AGNIS is an open source, peer-to-peer messaging service being developed by CIBMTR and NMDP for electronic exchange of clinical data. Centers will be

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SCTOD UPDATE

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able to electronically message clinical data directly from their database into FormsNet™, and CIBMTR will then be able to return each center's data to them for their own use, including their legacy data.

Messaging, security, and storage of clinical data require common data element definitions. When fully functional, AGNIS will allow robust exchange of these data elements locally and worldwide.

- One beta site is already successfully submitting selected forms to CIBMTR through AGNIS and several other centers are at various stages of becoming beta sites.
- Support for beta sites has been made available in several formats:
  - Application download and documentation available on www.agnis.net;
  - A Google group for exchange of highly technical support;
  - Weekly calls are ongoing between developers and beta sites.
- Curation of common data elements is in progress. This is a prolonged process.
  - Curation workflow was recently reviewed to improve efficiency of the process;
  - Automated tools and curation assistance were obtained from NCI.

A second Information Technology Summit was held in Minneapolis on September 2-3, 2009. The focus was more technical than the previous year's summit, dealing with data standards and interoperability. It was attended by approximately 135 participants, including IT staff, medical directors, data managers, and others.

Center volumes project

As mandated by the SCTOD contract, CIBMTR will use the data it collects to publish transplant center volumes data for 2008 on the C.W. Bill Young Cell Transplantation Program website at http://bloodcell.transplant.hrsa.gov. This will make HCT volume and demographic data by center accessible to the public and the transplant community.

Prior to publishing these data, transplant center representatives were asked to review their center's data for completeness and accuracy. This was the first external use of the Data Back to Centers application on the CIBMTR Portal (https://portal.cibmtr.org). The center volume reports will be available on the government website in the near future.

Cord blood data

Since formation of the Cord Blood Data Working Group last December, several of its goals have been accomplished to help Cord Blood Banks meet their reporting needs.

- Cord blood reports were redesigned to better meet cord blood bank needs.
- Consensus was reached on use of the FIN number to identify cord blood units.
- Investigation of cord blood reporting completeness, using bank-supplied listings of NMDP-facilitated and non-NMDP shipments, is being done monthly.
- A pilot project was instituted to compare thaw data from lab reports to data reported on CIBMTR Form 2006 (product data).
- Training opportunities are being implemented.

Additionally, a cord blood validation meeting was held in Minneapolis on Sept. 16, 2009, attended by bank and lab representatives as well as CIBMTR staff. Discussions included:

- A review of current validation processes, with a view to modifying processes based on subject matter expertise and flow of data once it is received by cord blood banks.
- Accurate identification of cord blood units, as there are many ID systems in place.
- Training opportunities for data managers regarding completion of infusion forms for cord blood units.
- Cord blood reports were restructured, with input from the Cord Blood Data Working Group, and are being distributed to centers on a routine basis.

Continuous Process Improvement

With the addition of CPI reporting tools to FormsNet in late 2009, CPI compliance goals will be re-implemented. The plan is to increase CPI expectations of teams over the next year for related donor and autologous data (unrelated data expectations of 90% compliance will remain unchanged).

Some other highlights of the past fiscal year include:

- The Data Back to Centers application was released to all U.S. centers in June 2009. It makes Pre-TED, Post-TED and Post-TED equivalent data elements available to transplant centers.
- Data Transmission Agreement and IRB return rates from U.S. centers were both greater than 90% by June 2009.
- The Related Recipient-Donor Pair Sample Repository had a total of 567 pairs at the end of June 2009.
- Thirty-five CPI audits were completed in fiscal year 2009. ■

RESOURCE FOR CLINICAL INVESTIGATIONS IN BLOOD AND MARROW TRANSPLANT (RCI BMT)

By Rebecca Drexler, Sr. Manager, Prospective Research

The RCI BMT collaboration with the Pediatric Blood and Marrow Transplant Consortium (PBMTC) continues to mature, as the PBMTC moves toward selection of the first trial to be run through the RCI BMT/PBMTC partnership.

The PBMTC was founded in 1989 and is comprised of more than 100 pediatric transplant centers in North America, Australia, and New Zealand. It is the largest clinical trials group focused exclusively on blood and marrow transplantation for children and adolescents. Working together, the RCI BMT and PBMTC will be able to address unmet needs in the field of pediatric marrow transplantation. We're excited to be a part of an effort that can make a big difference for kids in need of marrow transplants for both malignant and non-malignant conditions.

We are also pleased to welcome our new RCI BMT Scientific Director: Willis Navarro, MD, has headed up the program since July 2009, after accepting the reins from Marcie Tomblyn, MD. Dr. Navarro joined NMDP and CIBMTR in July of 2008, following nearly three years at Genentech, Inc. as a medical director in Avastin* Development and six years as a hematologist and transplant physician at the University of California, San Francisco.

** Avastin: generic name, bevacizumab, was the first angiogenesis inhibitor clinically available in the United States.* ■

CIBMTR SUMMARY SLIDES

By Marcelo C. Pasquini, MD, MS, and Zhiwei Wang, MS

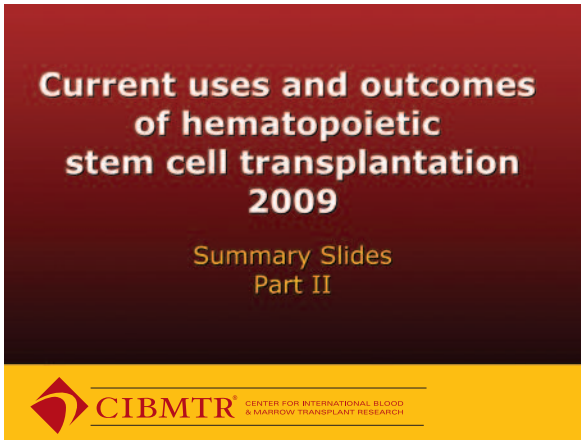
This second installment of the 2009 CIBMTR Summary Slides describes the statistical probabilities of survival for patients with the diseases most commonly treated with HCT. The data were derived from patients receiving transplants between 1998 and 2007, and reported to the CIBMTR. The survival curves are stratified by several factors: recipient age, donor type (i.e. autologous, human leukocyte antigen [HLA]-identical sibling, or matched-unrelated donor transplant), time from diagnosis to HCT, disease status or chemosensitivity at the time of the transplantation, and conditioning regimen intensity. However, comparisons do not adjust for other potentially important factors that may impact overall survival. Consequently, differences in outcomes between curves should be interpreted cautiously.

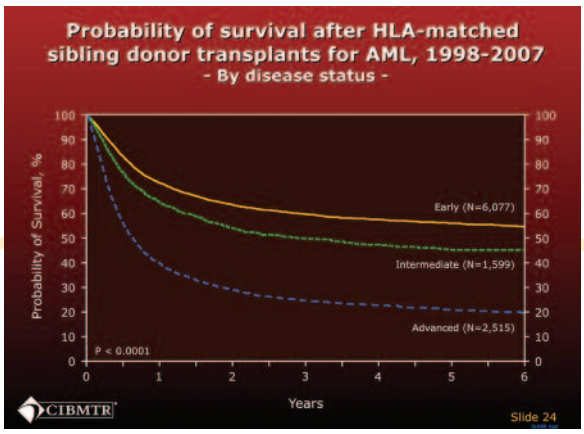
Acute myeloid leukemia (AML), acute lymphocytic leukemia (ALL), and chronic myeloid leukemia (CML) are classified as early (i.e. first complete remission [CR1] or first chronic phase [CP1]), intermediate (i.e. second or subsequent CR or CP or accelerated phase [AP]), or advanced (i.e. primary induction failure, active disease, or blastic phase) disease. Myelodysplastic syndrome (MDS) is divided into early (i.e. refractory anemia or refractory anemia with ringed sideroblasts), or advanced (i.e. refractory anemia with excess of blasts, or chronic myelomonocytic leukemia) disease. Lymphoma is classified according to sensitivity to prior chemotherapy (i.e. chemosensitive or chemoresistant).

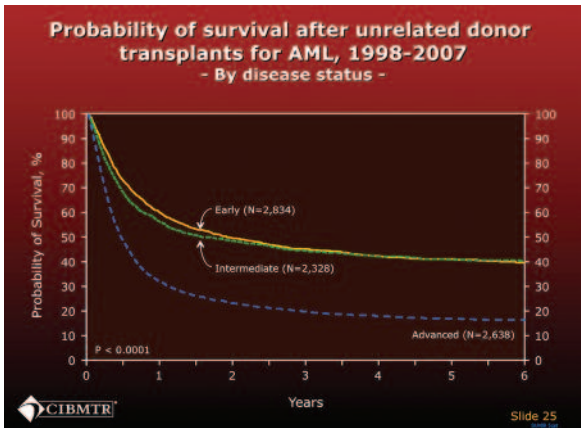
Preparatory regimen intensities are classified as myeloablative or reduced-intensity regimens, as reported by the transplant center. The CIBMTR uses the following operational definitions for regimen intensity. These operational definitions were applied to a subset of patients with available comprehensive data: Myeloablative conditioning regimen: regimens with total body irradiation (TBI) doses of ≥500 cGY, single fractionated doses of ≥800 cGY, busulfan doses of >9 mg/kg, or melphalan doses of >150 mg/m2 given as single agents or in combination with other drugs.Reduced-intensity conditioning regimen: regimens with lower doses of TBI, fractionated radiation therapy, busulfan, and melphalan than those used to define the myeloablative conditioning regimen.

Please use the following citation when utilizing data from these slides: Pasquini MC, Wang Z. Current use and outcome of hematopoietic stem cell transplantation: Part II-CIBMTR Summary Slides, 2009. CIBMTR Newsletter [serial online]. 2009;15(2):7-11.

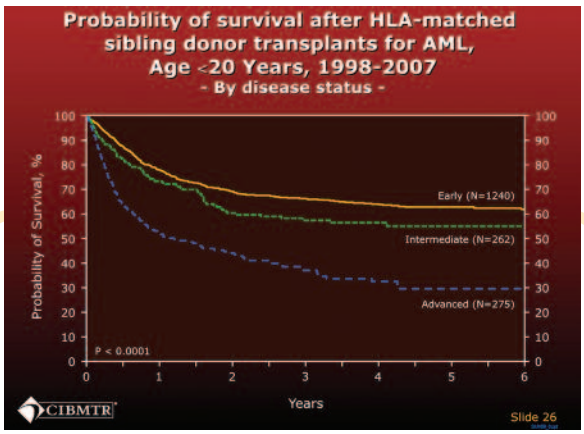
Available at: **http://www.cibmtr.org/PUBLICATIONS/Newsletter/index.html.** Accessed November 2009.



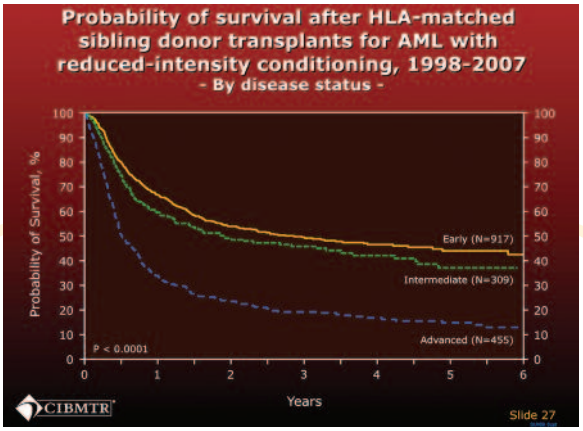


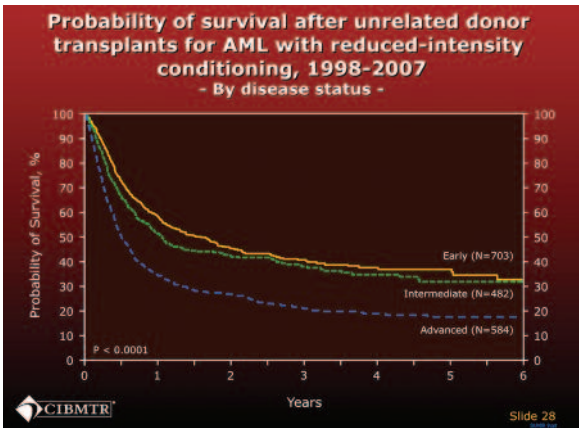


Slides 24 and 25: The CIBMTR has data for 17,991 patients receiving HLA-matched sibling (n=10,191) or unrelated donor (n=7,800) HCT for AML between 1998 and 2007. Disease status at the time of the transplant and donor type are the major predictors of post-transplant survival. The three-year probabilities of survival after HLA-matched sibling HCT in this cohort are 60% ± 1%, 50% ± 1%, and 25% ± 1% for patients with early, intermediate, and advanced disease, respectively. The probabilities of survival after unrelated donor HCT are 45% ± 1% for patients with early and intermediate disease and 20% ± 1% for patients with advanced disease.

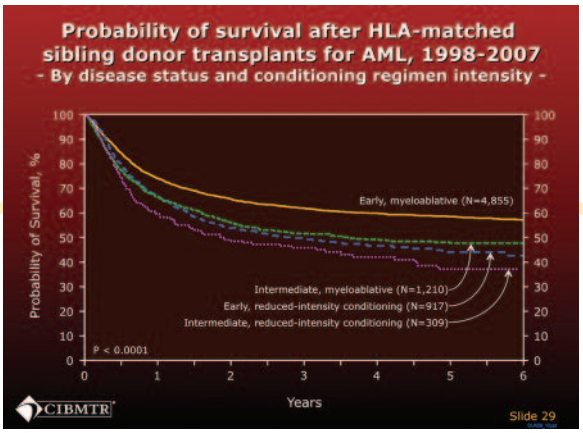


Slide 26: Among AML patients younger than 20, the three-year probabilities of survival following HCT for patients with early, intermediate, and advanced disease are 66% ± 2%, 58% ± 4%, and 37% ± 3%, respectively.

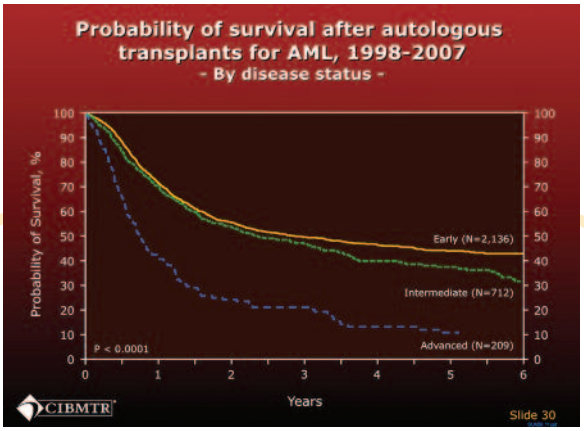




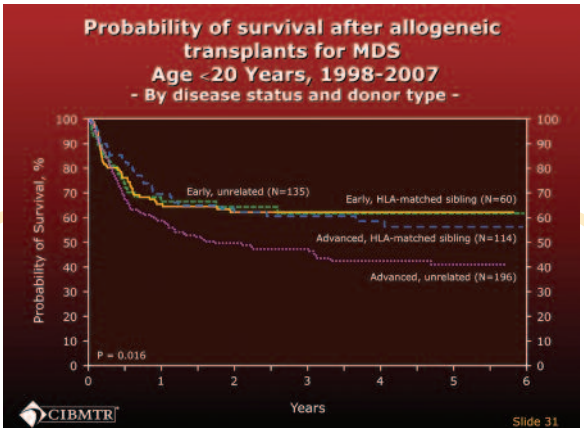
Slides 27 and 28: The three-year probabilities of survival for the 1,681 patients with AML who received transplantation with a reduced-intensity conditioning regimen from an HLA-matched sibling donor are 50% ± 2%, 46% ± 3%, and 19% ± 2% for patients with early, intermediate, and advanced disease, respectively. The probabilities of survival for the 1,769 recipients of unrelated donor allogeneic transplants are 41% ± 2%, 38% ± 3%, and 21% ± 2% for patients with early, intermediate and advanced disease.

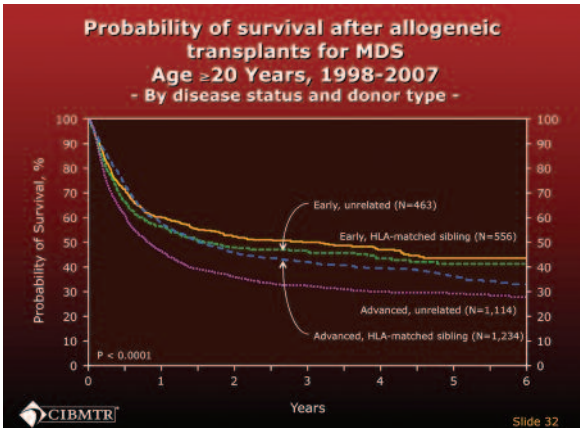


Slide 29: Reduced-intensity conditioning regimens are frequently used with patients older than 50 or who have comorbidities at the time of the transplant. Among AML patients who received an HLA-matched sibling HCT, the three-year probabilities of survival for patients with early and intermediate disease who received a reduced-intensity conditioning regimen were 50% ± 2% and 46% ± 3%, respectively. Among patients who received a myeloablative conditioning regimen, the probabilities of survival were 62% ± 1% in patients transplanted during CR1 and 52% ± 2% for those transplanted in a subsequent remission. Differences in age and other comorbidities were not adjusted in the groups analyzed in this slide.

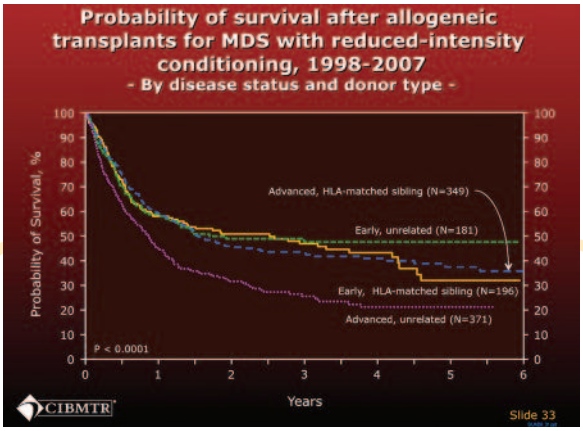


Slide 30: CIBMTR has data for 3,057 autologous transplants performed for AML between 1998 and 2007. The three-year probabilities of survival for patients with early, intermediate and advanced AML were 50% ± 1%, 47% ± 2%, and 21% ± 3%, respectively.

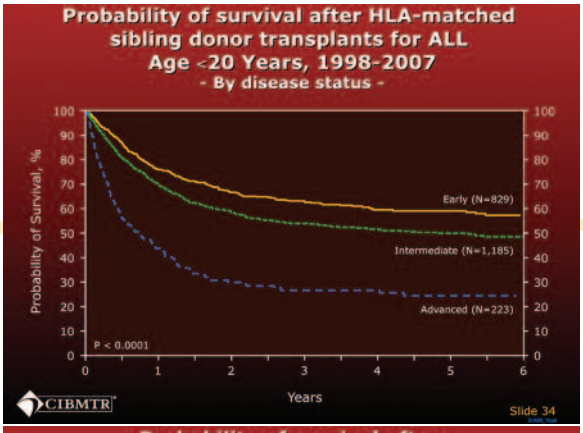


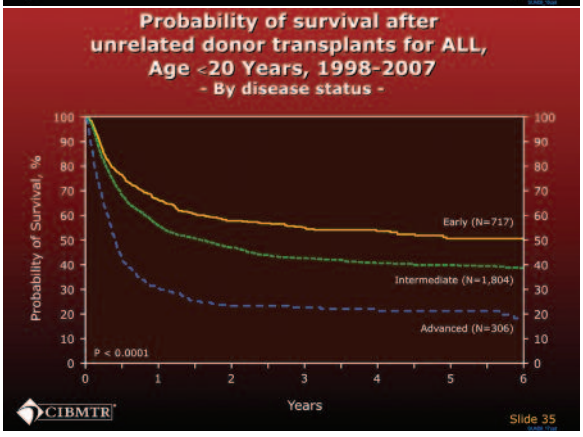


Slides 31 and 32: Allogeneic HCT is a potentially curative treatment for myelodysplastic syndrome (MDS). Outcomes differ according to the recipient's age, donor type, and disease status at the time of the transplant. Among 174 recipients of HLA-matched allogeneic HCT younger than 20, the three-year probabilities of survival were 62% ± 6% and 61% ± 5% for patients with early and advanced disease, respectively. The corresponding probabilities of survival in the 331 recipients receiving an unrelated donor HCT were 62% ± 4% and 47% ± 4%. Among the 1,790 patients 20 years receiving HLA-matched sibling HCT, the three-year probabilities of survival were 50% ± 2% and 42% ± 2% for early and advanced MDS, respectively. The corresponding probabilities in the 1,577 older patients receiving unrelated donor HCT were 46% ± 3% and 32% ± 2%.

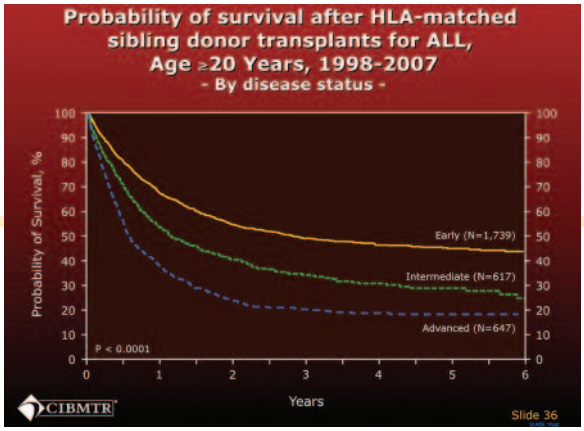


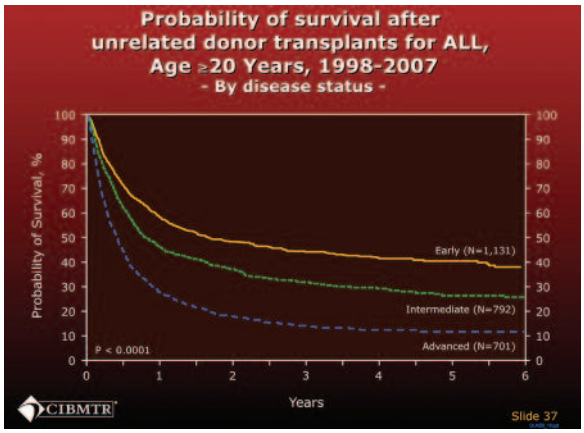
Slide 33: The median age of patients with MDS at diagnosis is 70 years, which limits the use of myeloablative conditioning regimens for most patients with this disease. Reduced-intensity conditioning regimens are increasingly used for allogeneic transplantation in MDS. Among 1,097 patients who underwent reduced-intensity conditioning allogeneic transplantation for MDS from 1998 to 2007, the three-year survival probabilities for recipients of HLA-matched donor transplants (N=455) were 47% ± 4% and 43% ± 3% for early and advanced MDS, respectively. Corresponding probabilities for recipients of unrelated donor transplants (N=552) were 48% ± 4% and 26% ± 3%.



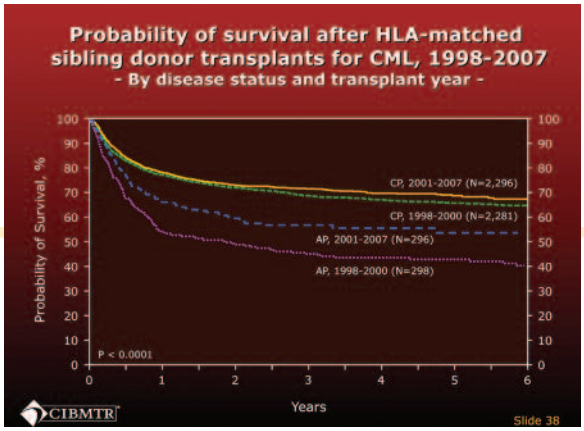


Slides 34 and 35: Among young patients with ALL, for whom chemotherapy has a high success rate, allogeneic transplantation is generally reserved for patients with high-risk disease (i.e. high leukocyte count at the time of diagnosis and the presence of poor-risk cytogenetic markers), who fail to achieve remission, or who relapse after chemotherapy. Among the 2,237 patients younger than 20 receiving HLA-matched sibling HCT, the three-year probabilities of survival were 63% ± 2%, 54% ± 2 %, and 27% ± 4% for patients with early, intermediate, and advanced disease, respectively. The corresponding probabilities of survival among the 2,827 recipients of unrelated donor HCT were 55% ± 2%, 43% ± 1%, and 23% ± 3%.

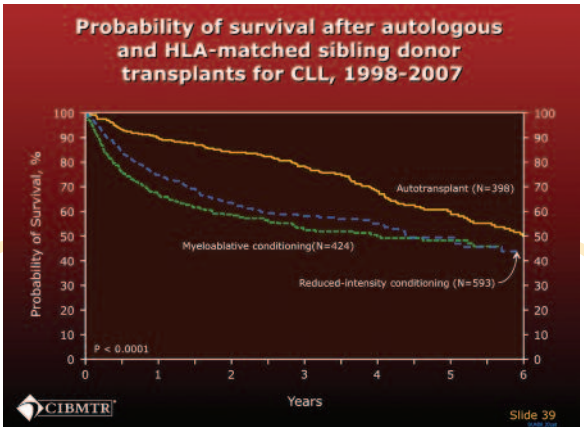




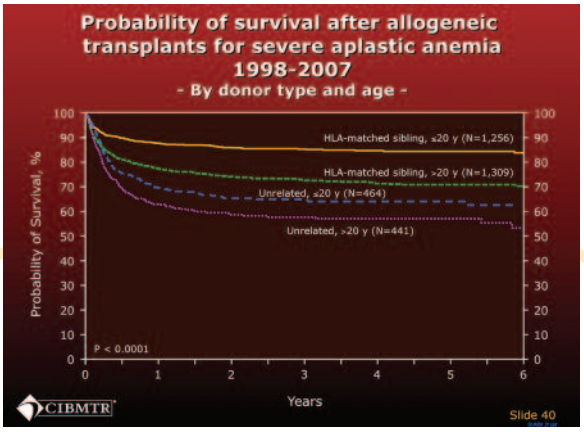
Slides 36 and 37: Older age at the time of disease onset is a high-risk factor in ALL. Consequently, a larger proportion of ALL patients 20 years of age or older undergo allogeneic HCT for early disease. Among 3,003 patients 20 years of age receiving HLA-matched sibling HCT, the three-year survival probabilities were 49% ± 1%, 34% ± 2%, and 20% ± 2% for patients with early, intermediate, and advanced disease, respectively. Corresponding probabilities among the 2,624 recipients of unrelated donor HCT were 44% ± 2%, 32% ± 2%, and 14% ± 2%.



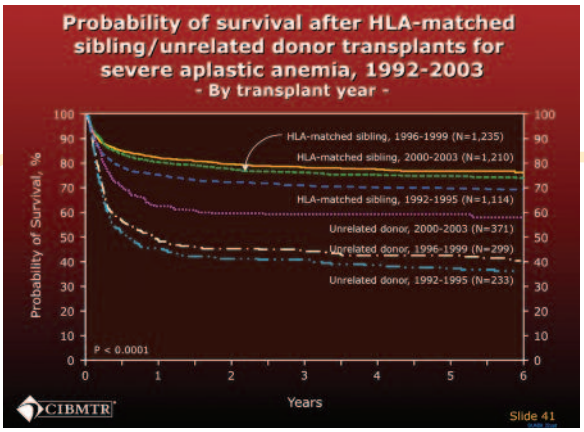
Slide 38: The annual numbers of patients undergoing allogeneic transplantation for the most common disease indications have changed over the past decade. While allogeneic transplantation for AML and ALL have steadily increased, allogeneic trans-plantation for CML has decreased. Tyrosine kinase inhibitors are currently the first treatment option for patients with newly-diagnosed CML, and allogeneic trans-plantation is reserved for patients who fail such therapy. CIBMTR has data for 5,171 HLA-matched sibling donor allogeneic transplants for CML patients in CP (n=2,440) and in AP (n=2,731) between 1998 and 2007. Among patients in CP, the three-year probabilities of survival were 69% ± 1% and 72% ± 1% for transplants in performed in the periods 1998 to 2000, and 2001 to 2007, respectively. Corresponding three-year survival probabilities for patients in AP were 45% ± 3% and 57% ± 3%.



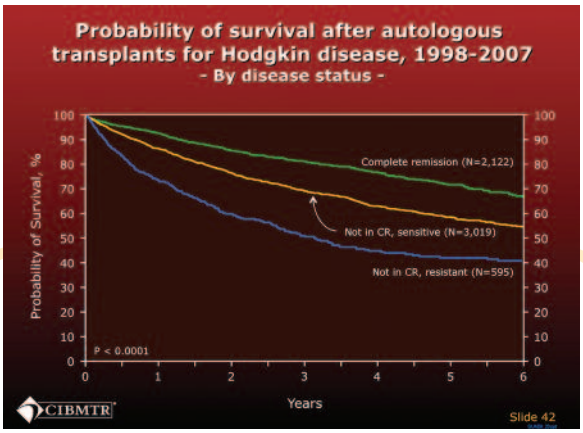
Slide 39: Both autologous and allogeneic HCT are treatment options for chronic lymphocytic leukemia (CLL) patients who fail standard chemotherapy or who have high-risk factors (e.g. cytogenetic abnormalities). The use of reduced-intensity conditioning regimens for allogeneic HCT continues to increase in this population. Among the 1,415 patients who underwent HCT for CLL, the three-year probabilities of survival were 78% ± 2% after autologous transplants, 53% ± 3% after HLA-matched sibling HCT with a myeloablative conditioning regimen, and 58% ± 3% after HLA-matched sibling HCT with a reduced-intensity conditioning regimen.



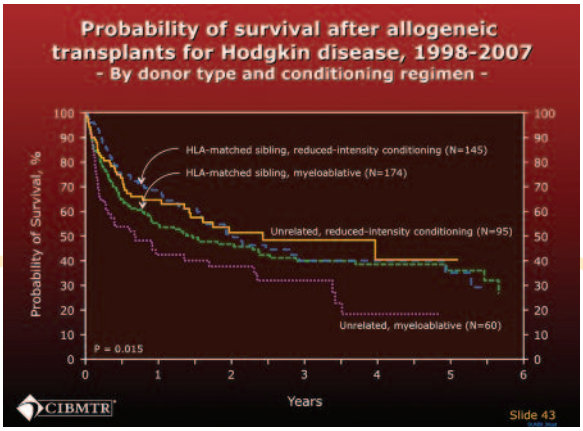
Slide 40: Allogeneic HCT is the treatment of choice for young patients with severe aplastic anemia (SAA) with an HLA-matched sibling donor available. Among the 2,565 patients receiving HLA-matched HCT for SAA between 1998 and 2007, the three-year probabilities of survival were 86% ±1% for those younger than 20 years and 73% ± 1% for those 20 years of age or older. Among the 905 recipients of an unrelated donor HCT, the corresponding probabilities of survival were 65% ± 2% and 58% ± 3%.



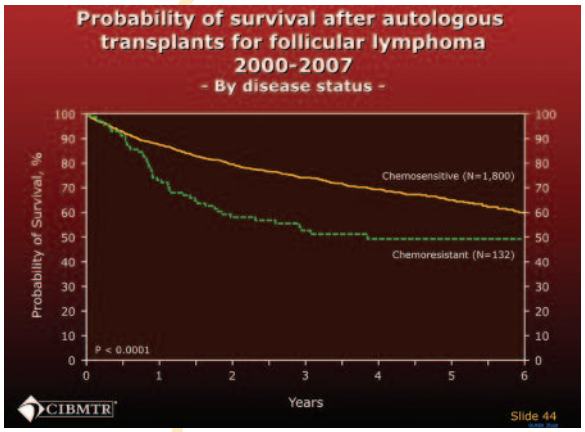
Slide 41: Survival probabilities for recipients of allogeneic HCT for SAA improved between 1992 and 2003. Among recipients of HLA-matched sibling donor transplants, the three-year survival probabilities were 71% ± 1%, 76% ± 1%, and 79% ± 1% in transplants performed in the periods from 1992 to 1995, 1996 to 1999, and 2000 to 2003, respectively. Corresponding survival probabilities for recipients of unrelated donor transplants were 41% ± 3%, 45% ± 3%, and 60% ± 3%. Better patient and donor selections, and improvements in supportive care contributed to the increased survival outcomes in this population.

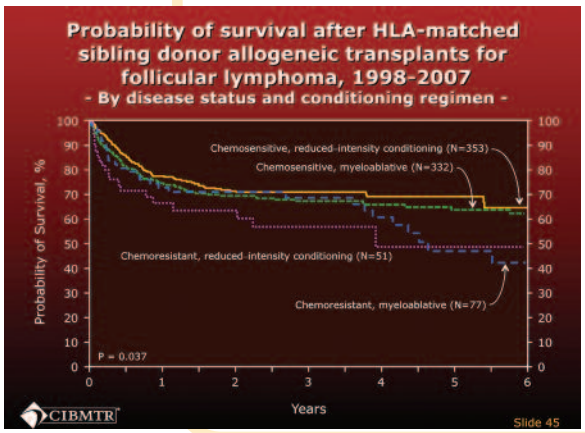


Slide 42: Transplantation for Hodgkin disease (HD) is indicated in patients who have failed initial chemotherapy or radiation therapy. Survival after HCT for HD depends on disease response to previous salvage therapy. Among the 5,736 patients receiving autologous transplants for HD between 1998 and 2007, the three-year probabilities of survival were 81% ± 1%, 69% ± 1%, and 51% ± 2% for patients in complete remission, in partial remission, and with chemoresistant disease, respectively.

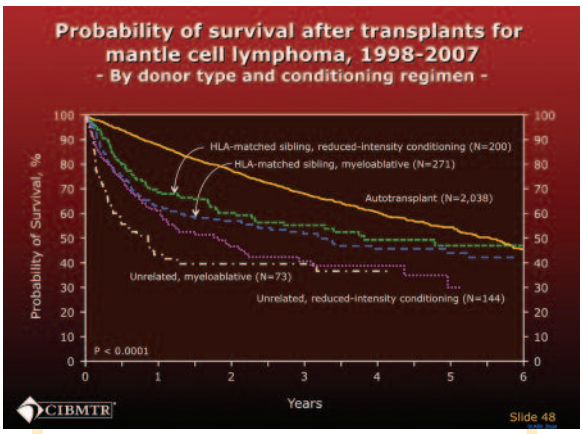


Slide 43: Allogeneic HCT for HD is generally performed in patients who experience disease relapse after receiving multiple lines of therapy, or who have refractory disease and an available HLA-matched donor. The use of reduced-intensity conditioning regimens in these heavily pretreated patients allows for a graft-versus-lymphoma effect with less regimen-related toxicity. Among 297 patients receiving HLA-matched HCT for HD between 1998 and 2006, the three-year probabilities of survival were 39% ± 5% with myeloablative conditioning regimens, and 38% ± 5% with reduced-intensity conditioning regimens. The corresponding probabilities of survival in the 138 recipients of unrelated donor HCT were 35% ± 7% and 46% ± 8%.

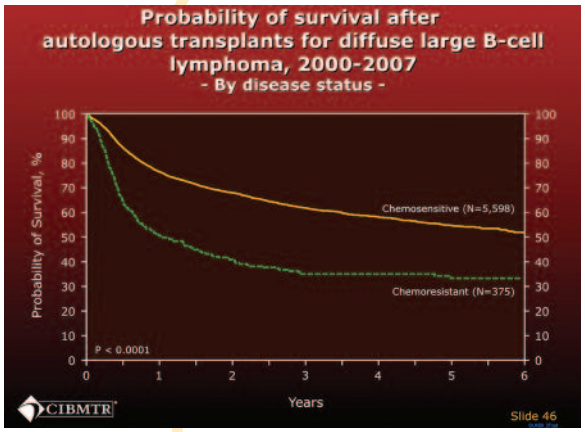


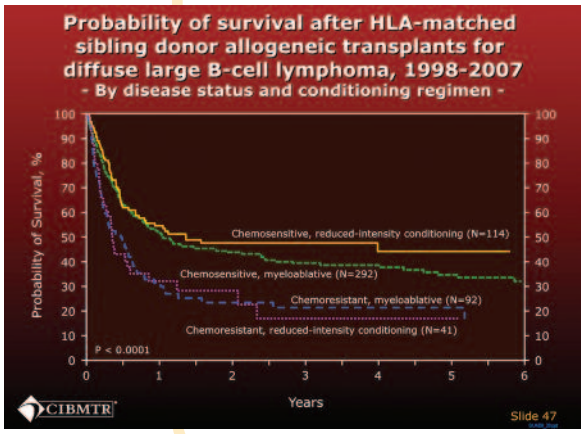


Slides 44 and 45: Transplantation for follicular lymphoma (FL) is generally reserved for patients with recurrent or aggressive disease. Autologous transplantation is the most common transplant approach in this disease. Among the 1,932 patients receiving an autologous transplant for FL between 2000 and 2007, most had chemosensitive disease. The three-year probabilities of survival were 75% ± 1% and 53% ± 5% for patients with chemosensitive and chemoresistant disease, respectively. Similar to CLL and HD, the use of reduced-intensity conditioning regimens is increasing for patients with FL. Among 813 patients with FL undergoing HLA-matched sibling donor allogeneic HCT between 1998 and 2007, the three-year probabilities of survival for patients with chemosensitive disease (N=685) were 68% ± 3% and 71% ± 3% for those receiving myeloablative and reduced-intensity conditioning regimens, respectively. Corresponding probabilities in the 128 patients with chemoresistant FL were 69% ± 6% and 57% ± 8%.

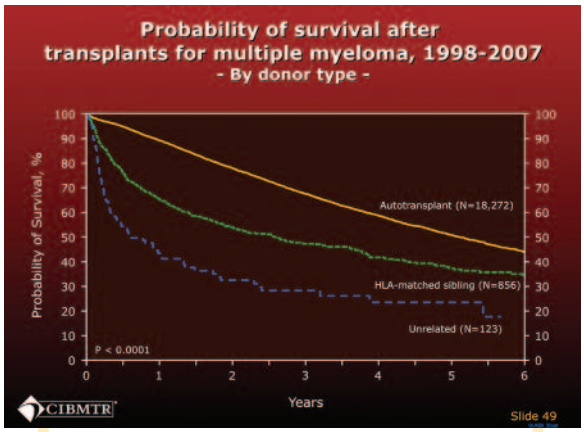


Slide 48: The optimal timing of HCT for mantle cell lymphoma (MCL) is not well defined. As with other mature B-cell lymphoproliferative disorders, autologous transplantation is the most common transplant approach. Among the 2,038 patients who received an autologous transplant for MCL between 1998 and 2007, the three-year probability of survival was 68% ± 1%. Among 688 patients who underwent an allogeneic transplantation for MCL during the same period, the three-year probabilities of survival for HLA-matched sibling donor transplants (N=471) were 52% ± 4% and 55% ± 4% for patients receiving myeloablative and reduced-intensity conditioning regimens, respectively. Corresponding probabilities for unrelated donor transplantation (N=217) were 40% ± 6% and 41% ± 5%.





Slides 46 and 47: Autologous transplants are an accepted treatment indication for diffuse large B-cell lymphoma (DLBCL) and, similar to FL, most autologous transplants are performed in patients with chemosensitive disease. Among the 5,973 patients who received an autologous transplant for DLBCL between 2000 and 2007, the three-year probabilities of survival were 62% ± 1% and 35% ± 3% for patients with chemosensitive and chemoresistant disease, respectively. Allogeneic HCT for treatment of DLBCL is performed less frequently than for FL, and is generally used only in patients with aggressive disease that has been resistant to previous therapies, including autologous transplants. Among the 539 patients who underwent an HLA-matched sibling HCT for DLBCL from 1998 to 2007, the three-year probabilities of survival for patients with chemosensitive disease (N=406) were 39% ± 3% and 48% ± 5% for patients receiving myeloablative and reduced-intensity conditioning regimens, respectively. The corresponding probabilities in the 133 patients with chemoresistant DLBCL were 21% ± 5% and 17% ± 8%.



Slide 49: Multiple myeloma (MM) is the most common disease indication for autologous HCT. Among 18,161 patients who received a single autologous transplant for MM between 1998 and 2007, the three-year probability of survival was 68% ± 1%. Allogeneic transplantation for MM is reserved for patients with high-risk disease, and the majority are performed after an autologous HCT with reduced-intensity or nonmyeloablative conditioning regimens. Among the 979 patients who received an allogeneic HCT from 1998 to 2007, the three-year probabilities of survival were 47% ± 2% for the 851 recipients of HLA-matched sibling donor transplants and 28% ± 5% for the 120 recipients of unrelated donor transplants.

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