CIBMTR™ CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

Newsletter

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High Resolution Donor HLA-Matching: Saving Lives

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Introduction

Each year, there are 30,000 individuals in the United States diagnosed with leukemia or another blood, metabolic, or immune system disorder requiring a hematopoietic stem cell transplant. Patients without an appropriate family donor turn to registries of volunteer donors for compatible stem cells. The U.S. National Marrow Donor Program (NMDP) in Minneapolis is the largest such registry, cataloguing more than 4 million donors. International exchange among donor registries worldwide increases the list of potential donors to >10 million.

The World Marrow Donor Association (WMDA) was founded in 1994 to facilitate the collection and transfer of unrelated donor hematopoietic cell products across international borders [1,2]. These registries provide patients without family donors an opportunity to receive a life-saving transplant.

High Resolution Typing of HLA Genes

A patient's outcome following transplantation depends upon many factors including age, disease severity, and the degree of match between donor and recipient for human leukocyte antigens (HLA) [3-30]. The commonly accepted definition of a matched donor is one who matches the recipient for the classical transplantation antigens, HLA-A, HLA-B, HLA-C, HLA-DR and HLA-DQ. Before DNA-based typing methods became available, studies defined donor-recipient HLA mismatching using serology. Serology was subsequently supplemented with polymerase chain reaction (PCR) technology which can distinguish unique alleles for the same serologically-defined antigen. New alleles are being discovered regularly (Figure 1). HLA allele sequences are named and standardized by the WHO Nomenclature committee [31] and catalogued in the IMmunoGeneTics (IMGT) database. For a given HLA locus (e.g., HLA-A), the gene variant at that locus is termed the allele (e.g., A*0201). Each HLA allele encodes a corresponding unique HLA protein or antigen (e.g. A2) expressed at the cell surface [32]. The combination of two antigens at a given locus, encoded by the alleles of two parental chromosomes, is termed the phenotype. Currently there are 451 known HLA-A alleles, 782 HLA-B alleles, 238 HLA-C alleles, and 438 HLA-DRB1 alleles. The definition of a matched donor continues to evolve with availability of more precise HLA typing methods.

Most typing methods used by clinical and research laboratories use PCR-amplification of specific HLA genes from genomic DNA. Direct determination of the entire coding region sequence of an allele can be accomplished with techniques such as sequencing-based typing (SBT) [33-38]. Other methods provide partial sequence information from which the allele is inferred; these methods include sequence-specific oligonucleotide probe hybridization (SSOPH) [39-49] or sequence-specific primer (SSP) typing [50-55]. Current SBT, SSOPH and SSP technologies utilize gene-specific amplification reactions and sequencing reactions with optimized primers and reaction formulations. Automated DNA sequencing is based upon fluorescent dye labeled dideoxynucleotide terminator chemistry. Sequencing reagents are, in most cases, similar in cost to other commercially available techniques such as SSOPH and SSP and the automated protocols may yield higher allele resolution at the same reagent cost. Standardized sequencing kits are able to improve sequencing quality by delivering PCR amplification and sequencing reagents that are normalized for sensitivity and specificity. Availability of commercial software for automated allele assignments is an integral part of a clinical laboratory's armentarium for efficient and precise HLA data analysis.

When a DNA typing method allows identification of a serologically-defined antigen-equivalent (e.g., HLA-A1 versus A2), the method is termed "low-resolution". SSOPH

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This issue of the CIBMTR Newsletter is made possible through an unrestricted educational grant from

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New Website: cibmtr.org

You may have noticed a change in our Web site. On December 1st, www.cibmtr.org went live with improved functionality and a streamlined design. You may download forms, find out how to propose a study, and learn more about the activities of the CIBMTR. Future additions to the Web site will focus on the work of the CIBMTR in prospective clinical trials, and the research conducted by the Working Committees. The site was created and is hosted by our research partner, the National Marrow Donor Program.

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approaches have flexibility in the resolution of HLA genes. They may employ a restricted number of probes and provide limited sequence information about a particular HLA gene, equivalent to that achievable by serology. Methods that define the HLA type beyond the serologic level but short of the allele level are termed "intermediate-resolution". For example, use of a wider array of probes for SSOPH typing might identify the presence of either HLA-A*0201 or 0205, but may not have informative probes to discriminate one allele from the other. This intermediate-resolution result would be characterized as "HLA-A*02" or "HLA-A*0201/05". When SSOPH and SBT methods provide nucleotide sequence information that allows identification of an HLA allele (e.g., HLA-A*0201), "high-resolution" typing is achieved. In order to interpret HLA typing results and select donors for transplantation, it is necessary to know whether the typing was done at low-, intermediate- or high- resolution, because a patient and potential transplant donor who are "matched" for HLA antigens by low-resolution typing methods may be mismatched for alleles at high resolution [49].

The importance of HLA matching and its impact on the clinical outcome of unrelated HCT emphasizes the need for high resolution typing capability for the final selection of a donor. At the same time, however, time constraints and the requirements for high-throughput typing technology must be considered, particularly in cases of high-risk unrelated transplant candidates who require the rapid identification of a suitable donor.

Genetics of Transplantation

Regardless of which technique is used, matching potential transplant donors and recipients at a high level of resolution is beneficial. High resolution matching may lower post-transplant complications of graft rejection, and acute and chronic GVHD [3,5,7,9,11,14,17,20,23,27]. For donor registries, use of DNA methods for high resolution typing may also provide the Registry with information needed to plan growth and recruitment of new donors [56,57,58,59].

Clinical experience shows that the risks of graft failure, GVHD and mortality increase with increasing numbers of HLA mismatches between the donor and recipient [3,5,17,27]. Additive or synergistic multilocus effects are observed with class I mismatches, class II mismatches, and combinations of class I and class II mismatches [3,5,17,27]. The largest comprehensive analysis of donor-recipient HLA matching to date was performed by the NMDP [27]. In this study, 1874 patients and their donors were typed for HLA-A, B, C, DR, DQ and DP alleles. The NMDP evaluated the impact of two levels of HLA matching: 1) high resolution matches defined as identical gene products, and 2) low resolution matches for which the first two digits of the allele name were converted to a "serologic equivalent". Low resolution mismatches at HLA-A, B, C and DRB1 each conferred increased risk of mortality. High resolution mismatches at HLA-A and DRB1 were also associated with increased death. The risk of grades III-IV acute GVHD was increased in the presence of HLA-A mismatching; a trend for higher acute GVHD risk was observed with HLA-B, C and DR mismatching.

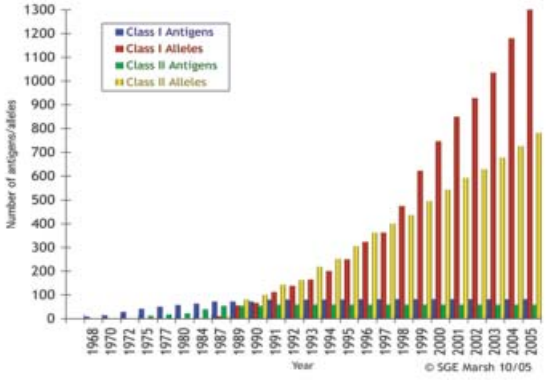

Figure 1. Increase in identification of HLA antigens and alleles named since 1968.

Figure 2A. Patients who were categorized as low-risk by pretransplant evaluation.

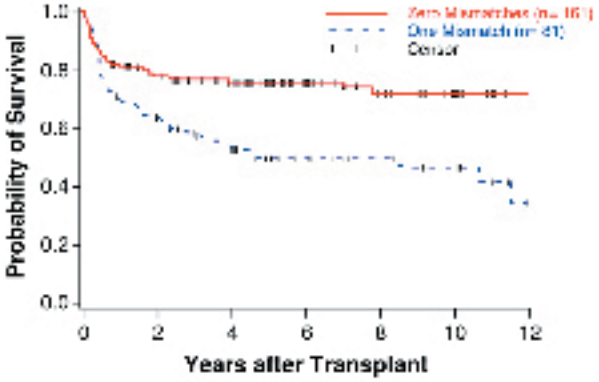

Figure 2B. Patients who were categorized as intermediate-risk by pretransplant evaluation.

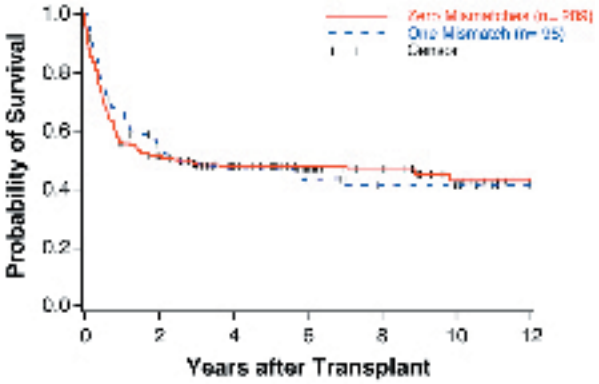

Figure 2C. Patients who were categorized as high-risk by pretransplant evaluation.

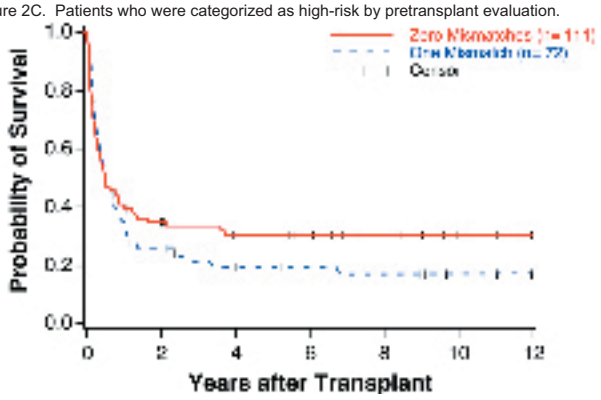

Figure 2. Kaplan Meier estimates of survival for patients according to the presence or absence of a single mismatch.

Three new findings can be summarized from this NMDP study. First, mismatches for HLA-A, B, C and DRB1 are similarly associated with increased risk of GVHD and mortality. This observation suggests that donor registries and search algorithms should pay additional attention to HLA-C in identifying potential donors. A second finding of this study was that high resolution mismatching, particularly at HLA-A and DRB1, increase mortality. This observation suggests that allele mismatches are functional and that high resolution DNA typing methods are needed to evaluate potential unrelated donors. Finally, the NMDP study found that low resolution mismatching was associated with higher mortality compared to high resolution mismatching. This observation has relevance to patients whose only donors are mismatched; selection of donors with high resolution mismatches over those with low resolution mismatches may lower posttransplant complications.

Optimal transplant outcome is associated not only with donor-recipient HLA matching, but also when transplantation can be performed with a low burden of disease. One recent study from the Fred Hutchinson

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Perspectives

By Sergio A. Giralt, MD

Associate Professor of Medicine, Hematology Co-Center Medical Director and Clinic Chief, MD Anderson, Houston, TX, USA

The Future of High Dose Chemotherapy and Hematopoietic Progenitor Cell Transplantation

The year 2006 marks the 50th anniversary of the seminal paper from Drs. Barnes and Loutit which demonstrated in the murine model the potential antileukemic effects of high doses of total body irradiation followed by donor bone marrow infusion. (Barnes DW, Corp MJ, Loutit JL, et al. Treatment of murine leukemias with x-rays and homologous bone marrow. British Medical Journal 2; 626-627; 1956.) During the ensuing 50 years many investigators and patients have literally dedicated their lives to fulfilling the initial expectations from that observation, which demonstrated that some malignant disorders could be cured through a combination of high dose therapy followed by hematopoietic stem cell rescue. We have all witnessed the dramatic changes that have happened in the way we perform and even conceive the procedure that was initially called bone marrow transplantation, and should be more precisely named hematopoietic progenitor cell transplantation.

Less than 20 years ago, the procedure was limited only to young patients, with good performance status. These limitations were necessary since only a young patient with few comorbidities could resist the intense chemo-radiotherapy administered, the ensuing 4 weeks of severe pancytopenia, and the emergence of multiple infectious complications for which only a small number of effective antibiotics were available. However, the last two decades have seen an explosion of new drugs and technologies that have made high dose chemotherapy and hematopoietic stem cell transplantation a safer and potentially more effective therapy. The advent of ganciclovir provided initially effective treatment and more importantly effective prophylaxis for CMV pneumonia (a major cause of transplant related mortality in the early 80's); the development of recombinant colony stimulating factors shortened the period of severe neutropenia from 24 days to 12 days, and allowed for the mobilization and collection of bone marrow stem cells from the peripheral blood. Transplantation of these peripheral blood stem cells shortened the period of neutropenia even further but rarely to less than 7 days. Other advances in supportive care (new antibiotics, antifungals and antivirals) have made the procedure safer and have allowed for expansion of the clinical indication to older and more debilitated patients with a variety of hematologic disorders.

The fact that the procedure may have become safer, does not mean that it is indicated for every patient in every circumstance. Despite the enormous logistic challenges that are involved in designing, implementing, conducting and analyzing randomized trials in bone marrow transplantation, the transplant community should congratulate itself on how many of these studies have been performed. The results of these studies have helped countless physicians and patients make better informed decisions over the role of high dose therapy and stem cell transplantation in their disease. Thus, today the large number of autografts performed for Non-Hodgkins Lymphoma, Multiple Myeloma, as well as allografts in first remission for acute lymphoblastic leukemia and acute myeloid leukemia are due in part to the event free survival and overall survival benefit shown for these procedures when compared to the standard therapies of the time.

The development of novel transplant therapies such as imatinib, lenalinomide, rituxmab among others, must always make us revisit the role progenitor cell transplantation plays in the treatment of any hematologic malignancy, and whether progenitor cell transplant outcomes could improve by incorporating some of these agents into the conditioning regimen or as part of planned maintenance therapy. The CIBMTR and the Bone Marrow Transplant-Clinical Trials Network will play essential roles in identifying current trends of use of progenitor cell transplantation as well as assessment of new transplant conditioning regimens and technologies through the performance of well designed retrospective and prospective studies. The designing and development of these studies as well as incorporating new knowledge emerging from the fields of cellular immunology, stem cell and cancer biology is what keeps our field interesting and full of vitality.

Today many of our colleagues believe that in the near future high dose therapy with progenitor cell transplantation as performed today will be replaced. I wholeheartedly agree. I expect the field to continue to move as rapidly as it has over the next 20 years, and none of us desire to be treating myeloma patients with melphalan 200 mg/m2 and unmanipulated stem cells 20 years from now. I do expect, that as we have done over the last 50 years, we will continue to be in the forefront of translational research now not only in hematology and oncology, but also in the newer field of regenerative medicine. My expectations are that with the incorporations of new agents and technologies currently in development or in phase I/II trials we will be able to reduce the risk of relapse post transplant, minimize toxicities, and eventually effectively separate graft versus tumor from graft versus host effects. The CIBMTR and the BMT-CTN will play an important role in making this vision a reality sooner rather than later, and by participating in their efforts through data contribution, study participation and proposals we are also part of this reality.

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Cancer Research Center (FHCRC) analyzed the impact of donor HLA mismatching according to the stage of disease at the time of transplantation to address whether there are circumstances in which HLA mismatch effects are offset by the effects of disease stage [29] (Figure 2). This analysis included 948 patients who received a T-replete unrelated hematopoietic cell transplant for treatment of a marrow disorder. The data were analyzed according to whether there was a single detectable HLA mismatch, or multiple mismatches, among patients with low versus intermediate versus high risk disease stage at the time of transplantation.

There was no statistically significant association between mismatching and outcome in intermediate- or high-risk groups for either relapse or transplant-related mortality (TRM). In contrast, a single HLA mismatch conferred a statistically significantly increased risk of TRM in low-risk patients. In low-risk transplants, the hazard of mortality was similarly detrimental among patients with a single allele mismatch and among those with a single antigen mismatch. Among all donor-recipient pairs with at least two HLA mismatches, patients transplanted from donors with HLA-DQB1 mismatching had increased mortality.

Both the NMDP and the FHCRC studies demonstrate the importance of matching at low-resolution, and avoidance of multiple mismatches. Furthermore, the use of high-resolution methods may help to detect allele mismatches between donors and recipient who have the same low-resolution typing; when multiple allele mismatches are present, both the NMDP and the FHCRC studies found increased risks of mortality. Currently there is no consensus as to whether certain combinations of mismatches should be avoided and how best to select among donors who have multiple HLA mismatches. The FHCRC data suggests that avoidance of multiple mismatches that include HLA-DQ

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2006 BMT Tandem Meetings Break Records in Honolulu!

By D'Etta Waldoch, CMP

Leading authorities from around the world experienced *a spirit of aloha* along with presentations of the latest developments in blood and marrow transplantation at the Hawaii Convention Center in Honolulu for the 2006 BMT Tandem Meetings, February 16-20, 2006. Scientific Program Chairs were Claudio Anasetti, MD (Tampa) for ASBMT and Olle Ringdén, MD, PhD (Stockholm) for CIBMTR.

Registration for the five-day continuing medical education (CME) conference and peripheral conferences (including BMT pharmacists, clinical research professionals, administrative and medical directors and oncology nurses) was 2,030—a 25 percent increase over last year's record. Attendees represented 43 countries, including 139 from Japan, Australia, South Korea and 10 other Pacific Rim countries.

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.

A record 510 abstracts, up 50% from 2005, submitted by investigators in 35 countries were accepted for oral and poster presentation for the 2006 Meetings. Abstracts were published in the February 2006 issue of Biology of Blood and Marrow Transplantation (Vol. 12, No. 2, Supplement). They are also indexed and accessible online through the CIBMTR and ASBMT Web sites (www.cibmtr.org and www.asbmt.org). Recipients of the CIBMTR Best Abstract Awards for Clinical Research were Catherine Bollard, MD (Houston), George McDonald, MD (Seattle) and Olle Ringdén, MD, PhD (Stockholm). Recipients of the ASBMT Best Abstract Awards for Basic Science Research were Michael Albert, MD (Munich), Lia Perez, MD (Tampa) and Seitaro Terakura, MD (Nagoya).

Also available online for purchase are audio CDs, MP3 files and CD-ROMs with PowerPoint visuals for plenary and concurrent scientific presentations and oral abstract sessions, and recordings of satellite symposia and the peripheral conferences.

Conference attendees were encouraged to attend and actively participate in 17 CIBMTR Working Committee meetings throughout the week. Working Committees review the past year's research accomplishments, discuss current CIBMTR studies and set the scientific agenda for the coming year.

2007 BMT Tandem Meetings – February 8-12 in Keystone, CO

Detailed information about the 2007 BMT Tandem Meetings at the Keystone Conference Center in Colorado will be continuously updated online on the CIBMTR (www.cibmtr.org) or ASBMT (www.asbmt.org) Web sites. Conference registration, hotel and condominium reservations and the abstract submission program (abstract deadline October 3, 2006) will go live in August via the Web sites. Register and book your flights early to get the best discount airfares. Plan to combine educational sessions and committee meetings with rest and recreation time in breathtaking Summit County.

Questions regarding support opportunities at the 2007 BMT Tandem Meetings, or for post meeting attendee mailing labels for the 2006 Meetings, may be directed to Sherry Fisher at 414-456-8897 or slfisher@mcw.edu.

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might be beneficial. Further analysis of multi-locus mismatching in a larger transplant experience will be needed to evaluate whether certain combinations of mismatching should be avoided. The NMDP and CIBMTR are currently conducting such a study under the leadership of Drs. Stephanie Lee and Claudio Anasetti.

The importance of HLA-A, B, C, and DR in transplantation has been well described; however, there have been conflicting results as to the clinical significance of HLA-DQ and HLA-DP [5,13,17,18,22,25,26,27,60,61,62]. Part of the seemingly different conclusions drawn from retrospective studies may be related to the different study questions and comparison groups used to measure differences in outcome associated with matching for these genes. Another challenge in HLA research is the occurrence of linkage disequilibrium (LD) between HLA loci. Strong LD between two loci favors high degrees of matching at both loci, whereas weak LD results in higher rates of mismatching for one or the other locus, as is the case with HLA-DP [63]. Hence, measurement of true independent effects conferred by a given locus requires very large numbers of transplants.

Many studies have elucidated the importance of donor-recipient HLA matching in early posttransplant complications. With a larger transplant experience and maturity of longitudinal data, it is now possible to evaluate late effects conferred by donor HLA matching [4,64]. An association of donor HLA mismatching with prolonged immunosuppressive therapy for chronic GVHD, compared to HLA matching, has been described in unrelated donor transplants; lower rates of discontinuation of immunosuppressive agents, more prolonged treatment, and higher non-relapse mortality are all long-term consequences of donor HLA mismatching [4].

Conclusion

The presence of high resolution HLA mismatches, the additive effects of multi-locus mismatches, and the pre-transplant disease stage all influence the success of hematopoietic cell transplants from unrelated donors. For patients who do not have matched donors, the judicious timing of transplantation with selected HLA mismatches that do not compromise the success of transplantation, may allow all patients in need of a transplant the opportunity to benefit from this treatment modality. Efficient and precise donor HLA typing by clinical laboratories provides a critical platform in support of allogeneic hematopoietic stem cell transplantation.

References

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2 Hurley CK, Raffoux C, on behalf of the World Marrow Donor Association. World Marrow Donor Association: international standards for unrelated hematopoietic stem cell donor registries. Bone Marrow Transplant 34:103-110, 2004.

3 Petersdorf EW, Gooley TA, Anasetti C, Martin PJ, Smith AG, Mickelson E, et al. Optimizing outcome after unrelated marrow transplantation by comprehensive matching of HLA class I and II alleles in the donor and recipient. Blood 92:3515-3520, 1998.

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Report on state of the art in blood and marrow transplantation –

This issue of the CIBMTR Newsletter brings you Part I of our annual report on the "State of the Art" in hematopoietic stem cell transplantation (HSCT). Using data submitted by our participating centers, this report summarizes current use and outcomes in HSCT. The report is written by Dr. Marcelo Pasquini who recently joined the CIBMTR staff.

Part I of this report focuses on trends in the use of HSCT – indications, recipient age, graft sources and transplant regimens.

Part II, which will appear in the next issue of the newsletter, will summarize outcomes of transplants focusing on survival. The annual report, distributed widely through our Website (www.cibmr.org), this newsletter and a compact disc provided free of charge to participating centers, represent a part of the CIBMTR's effort to make the data contributed by transplant centers accessible to the transplant commmity. We hope you find it useful, and welcome suggestions to make future editions even better.

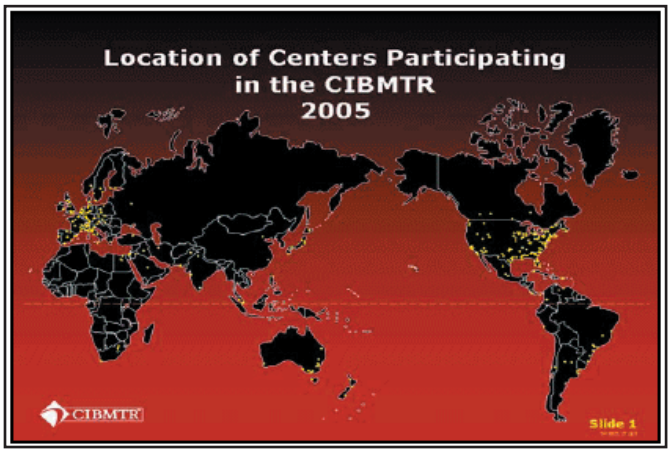
Part I – CIBMTR Summary Slides, 2005

By Marcelo Pasquini, MD

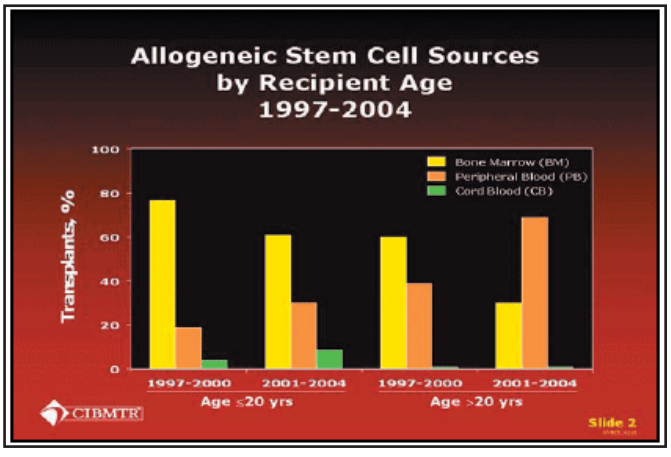
Assistant Professor, CIBMTR, Medical College of Wisconsin, Milwaukee, WI, USA

The annual number of hematopoietic stem cell transplants fluctuated considerably in the last two decades. After a period of steady growth, there was a sharp drop in the number of autotransplants toward the end of the 1990's, reflecting decreased use of this strategy for the treatment of breast cancer. The number of allotransplants also decreased to a lesser extent during the same period as a result of the use imatinib mesylate for the treatment of chronic myelogenous leukemia. This change was offset by the increased number of allotransplants with reduced intensity conditioning in older patients not previously considered transplant candidates. Additionally, there was an increase in cord blood transplants, mainly in the pediatric population. Estimates of the annual number of hematopoietic stem cell transplants in North America and worldwide included in these slides were extrapolated from data compiled by the National Marrow Donor Program (NMDP), the European Blood and Marrow Transplant Group (EBMT) and the CIBMTR.

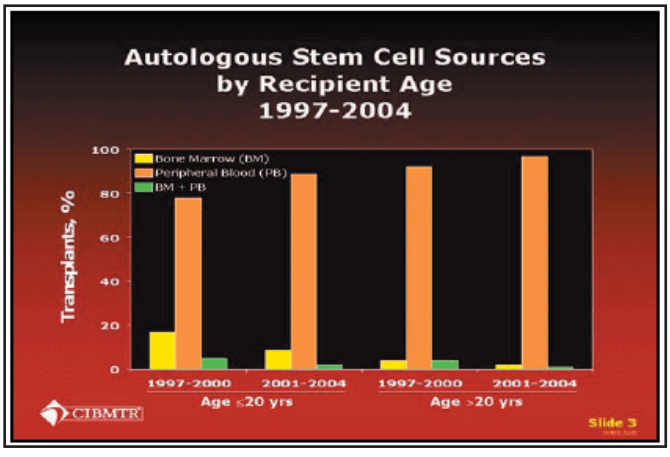
Slide 1: With the research affiliation between IBMTR/ABMTR and NMDP, the CIBMTR now has expanded its representation to more than 500 centers from 54 countries worldwide.

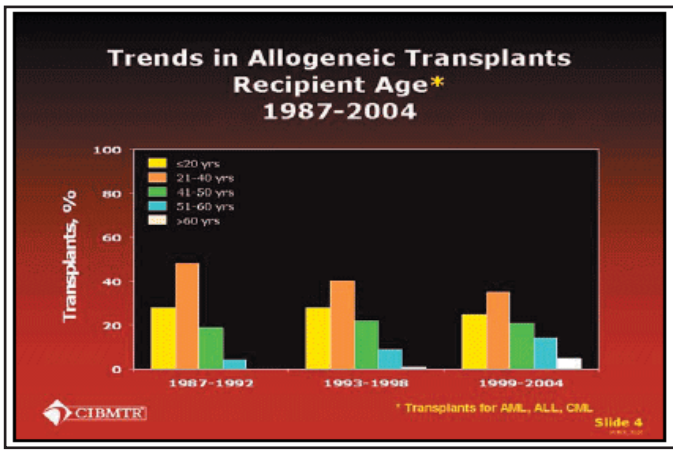


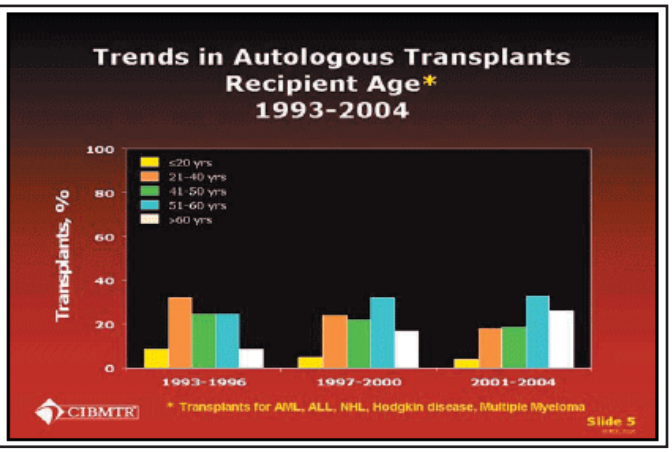
Slide 2: Bone marrow is the primary graft source for allogeneic transplantation in the pediatric population. During 2001 to 2004, peripheral blood stem cells and cord blood grafts became more common in children, accounting for 40% of transplants. Among adults, peripheral blood is now the main stem cell source. Use of cord blood grafts in adults is still uncommon.



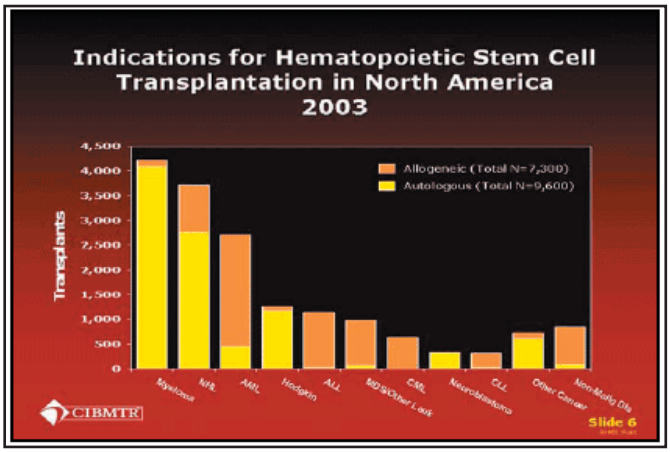
Slides 3: Currently, most autotransplants use mobilized peripheral blood hematopoietic stem cells transplantation, regardless of patient's age.

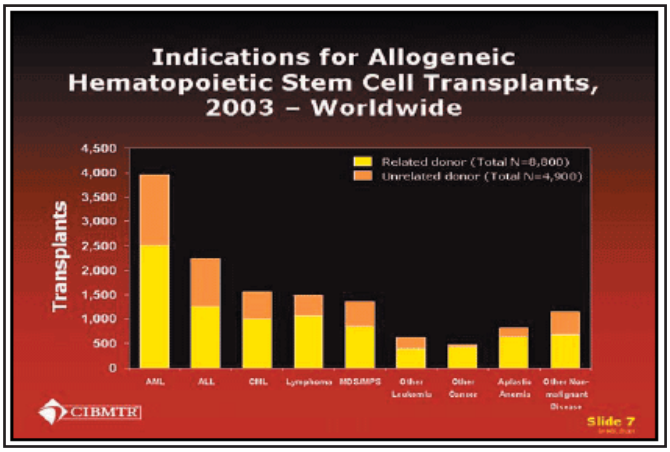






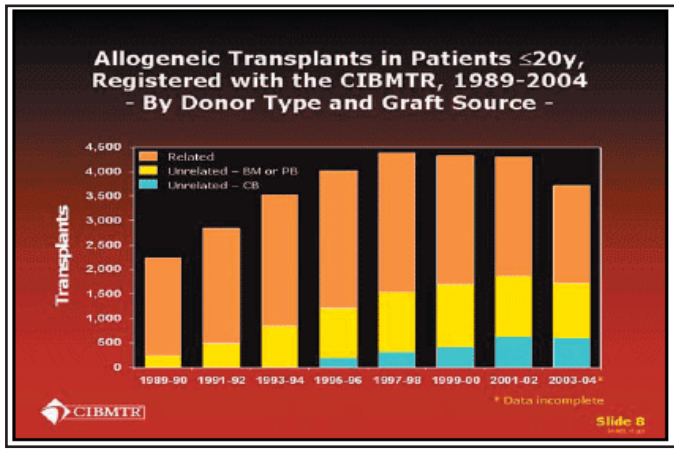
Slides 4 & 5: For both autologous and allogeneic hematopoietic stem transplantation, the average age of recipients has increased in recent years. Widespread utilization of reduced intensity conditioning regimens in the setting of allogeneic transplantation and overall improvement in supportive care are responsible for this trend. Fifty-nine percent of patients who received an autotransplant and 19% who received an allotransplant in 2001 to 2004 were older than 50 years of age; corresponding percentages of recipients older that 60 years were 26% and 5% respectively.

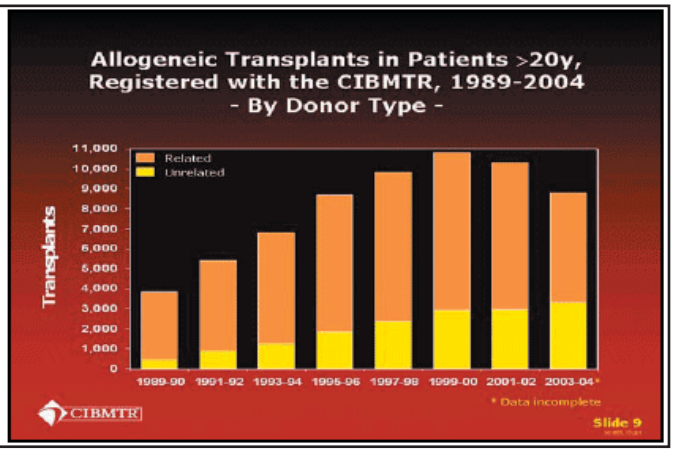




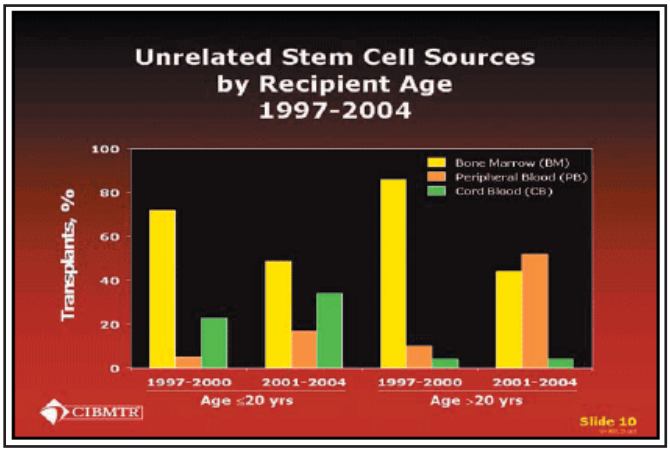
Slide 6: The most common indications for autologous transplantation in North America in 2003 were multiple myeloma and lymphoma, accounting for an estimated 8,000 transplants. The most common indications for allogeneic transplantation in North America were leukemia and myelodysplasia, accounting for an estimated 5,000 transplants.

Slide 7: Greater than one third of all allogeneic transplants are from unrelated donors. The use of donors other than HLA-identical siblings depends on the disease indication (and related efficacy of alternative therapy), age of the patient and lack of related donors. Patients with acute leukemias are the most likely to be considered for unrelated allografts. The proportion of transplants for acute leukemia that are donated by unrelated volunteers is now about 40%.

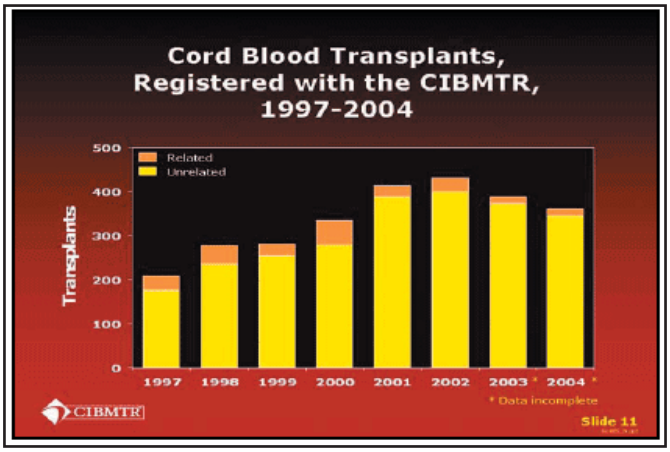




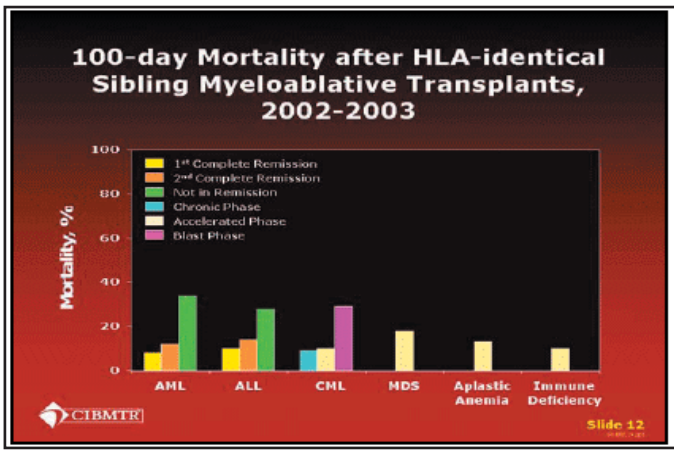
Slide 8 & 9: The overall number of transplants in patients younger than 20 years is relatively unchanged since 1997. However, the proportion of these from unrelated donors has increased. Among patients above 20 years, the introduction of imatinib mesylate for the treatment of CML has resulted in a modest decrease in use of allografting. Even among adults, however, the proportion from unrelated donors has increased.

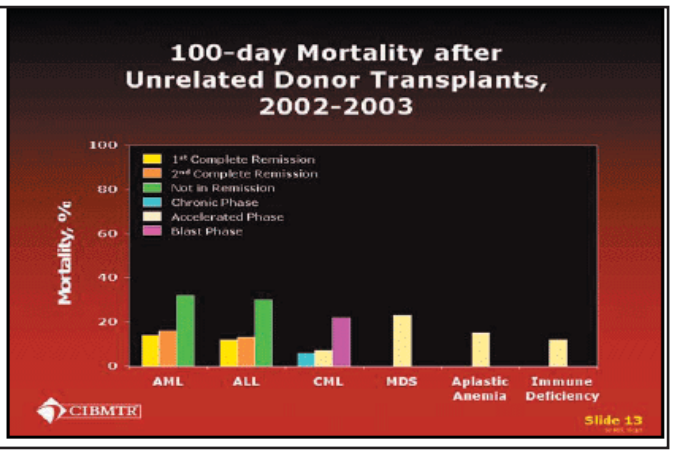


Slide 10: The graft source used for unrelated donor transplantation has changed significantly over the past decade. Bone marrow was still the main graft source for unrelated transplantation in recipients younger than 20 years; however, more than one third of these patients received umbilical cord blood grafts. Among adults, mobilized peripheral blood hematopoietic stem cells are the most common graft source for unrelated donor transplants.



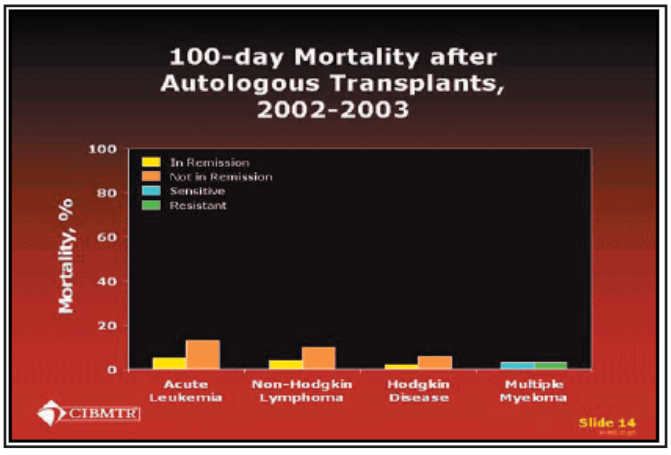
Slide 11: Most cord blood transplants are from unrelated donors. No specific trends in the number of related cord blood transplant are evident. Fewer than ten autologous cord blood transplants were registered with the CIBMTR from 1997 through 2004.



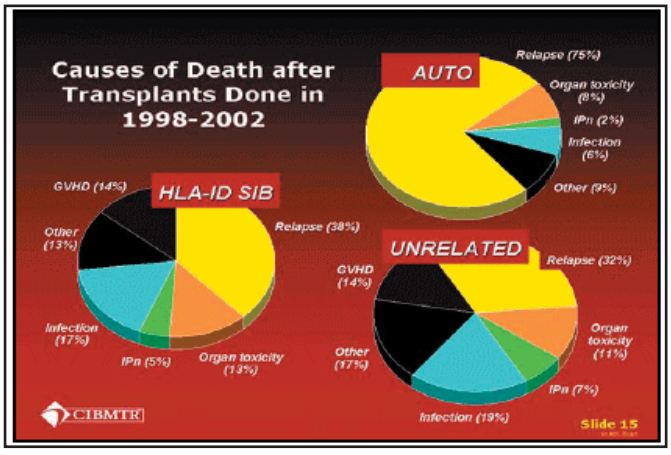


Slides 12 & 13: One hundred-day mortality is often considered a surrogate for transplant-related toxicity though primary disease and disease status at time of transplant significantly affect early post-transplant survival. For instance, patients transplanted for acute leukemia in remission with an HLA-identical sibling donor have 100-day mortality rates of 8 to 14% compared to 30% in patients with active disease at transplant. The causes of death at 100 days post transplant are mainly related to graft versus host disease (GVHD), infection and organ toxicity damage. Patients with active disease at transplantation have, in addition, a higher risk of early disease relapse, which contributes to excess mortality in this patient group.

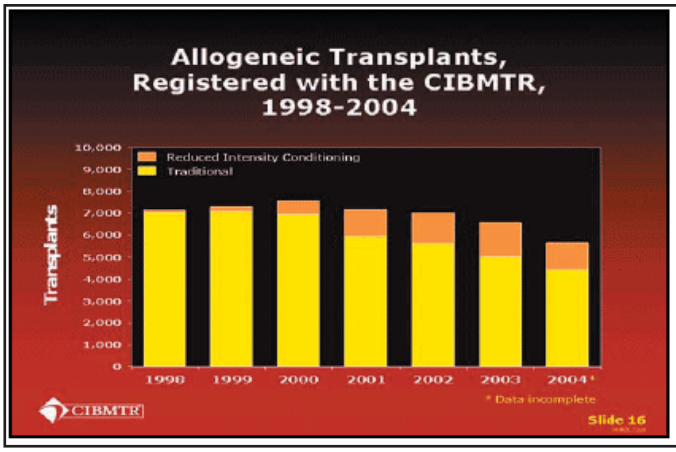
The mortality rates at day 100 after unrelated donor transplants are slightly higher than after HLA-identical sibling transplantation.

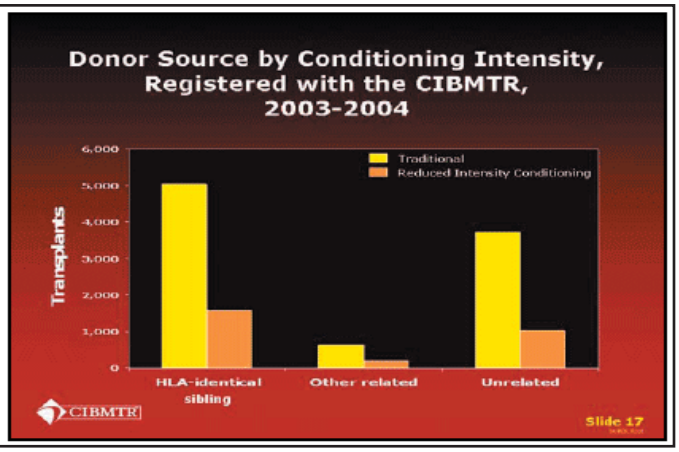


Slide 14: The 100-day mortality rates after autotransplantation is much lower than after allogeneic transplantation. It is also influenced by primary disease and disease status at autotransplantation.

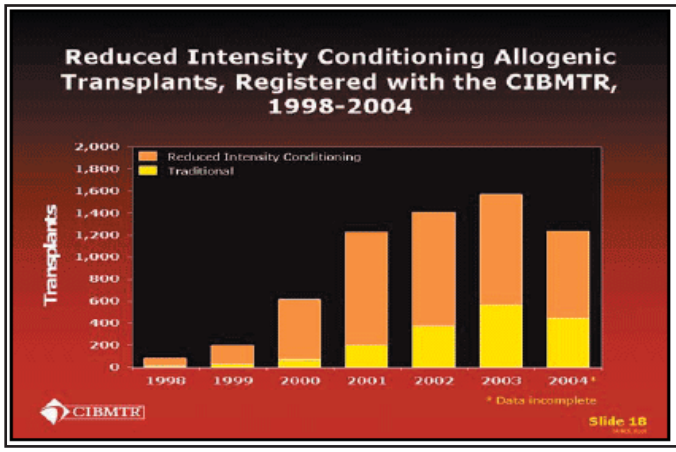


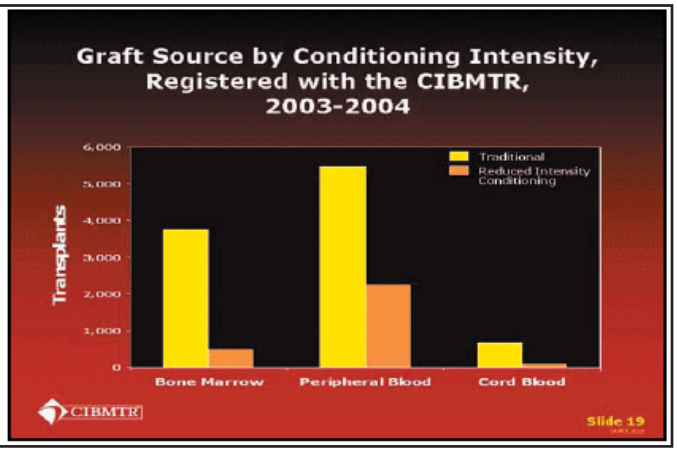
Slide 15: Relapse remains the primary cause of death after autotransplantation. In the allotransplant setting, GVHD, infection and organ toxicity predominate.

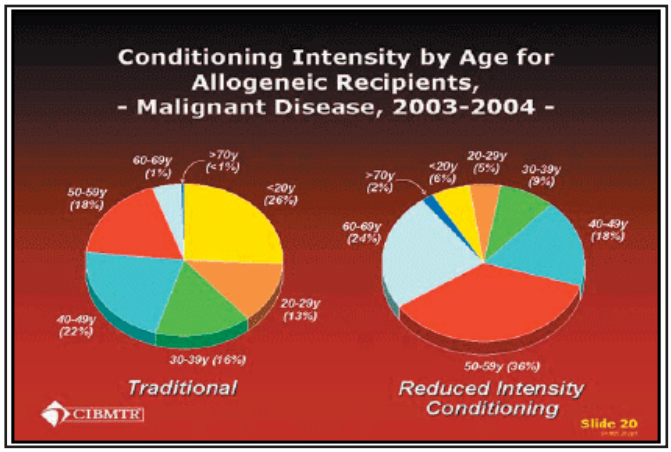


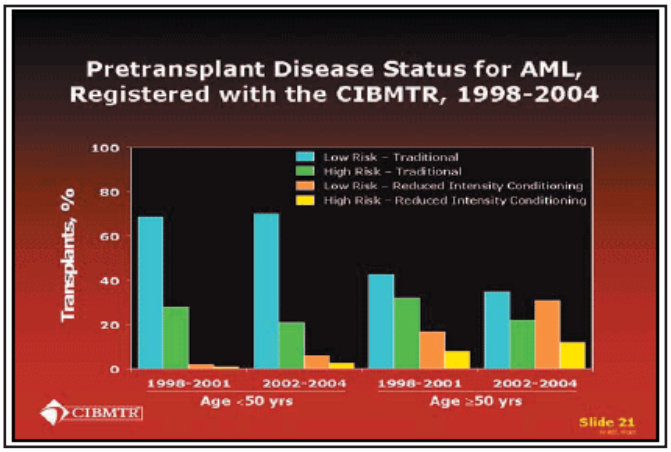


Slides 16 to 19: The median age at diagnosis for most considered indications for transplantation is above 55 years. Many of these patients are not considered suitable candidates for transplantation because of age-related increases in risks of toxicity from intensive pretransplant conditioning. Reduced intensity conditioning regimens have been recently introduced to decrease this risk and now account for about 30% of allogeneic transplants. Reduced intensity conditioning transplants numbers are based on the individual transplant center's designation at registration that the pretransplant conditioning regimen was non-myeloablative or reduced intensity.









Slide 20: More than 60% of patients receiving reduced intensity regimens are older than 50 years compared to less than 20% of traditional transplant recipients.

Slide 21: Among patients with acute myeloid leukemia older than 50 years, the number receiving a reduced intensity conditioning regimen now approaches the number receiving conventional conditioning. Younger patients are less likely to received reduced intensity conditioning. (*Low risk: patients in any complete remission; High risk: patients with active disease at transplant or primary induction failures.)

AGNIS: Help for Data Management

By Dennis Confer, MD

Chief Medical Officer, National Marrow Donor Program, Minneapolis, MN, USA

Data management in clinical medicine is a huge issue, and the transplant community is affected perhaps more than most others. No legitimate transplant program can operate today without a system for the collection, storage, retrieval and sharing of data. Everybody it seems wants data from the program - the hospitals that house the operations, the payers whose clients are treated there, the prospective patients themselves, the sponsors of clinical trials, and the transplant registries, like the CIBMTR and the NMDP. The transplant program itself requires its own data to adequately assess experiences, successes and shortcomings, as well as to support its own research programs.

Many of us who request data are "kind enough" to provide a form – oftentimes a very long and complex form - one that we have spent months or years designing and maintaining in order to meet our individual needs. These multiple forms require that the same, or similar, data are entered over and over again creating additional hardships for the data management team. Given that these data are so critical, it's a bit of a surprise that data management is routinely under-funded. Although everyone seemingly wants data, no one appears willing to bare the full cost of data management. The demands for data and the willingness to pay for it have not stayed in balance.

So what are the solutions for the increasing burden of data management? Certainly one approach is to reduce the numbers of differing forms. Later this year, the CIBMTR and the NMDP will introduce a single set of co-sponsored data forms – a single set of forms and one set of instructions for their completion. This we believe is a clear step in the direction of easing the data management burden.

But there are additional, potentially more far reaching approaches for novel data management. One of these is exemplified in a project called AGNIS. AGNIS, an acronym for "A Growable Network Information System," is a research effort jointly conducted by the CIBMTR and the NMDP. The AGNIS project is funded by a contract from the National Institutes of Health that is part of the NIH Roadmap Initiative, which seeks to reengineer clinical research activities in the U.S. (see nihroadmap.nih.gov).

So, what is AGNIS? Simply stated, AGNIS is a system for automated data exchange. AGNIS is a messaging system that runs largely behind the scenes to move data from one computer database into another. AGNIS represents an extension of a very successful messaging system, EMDIS, that was initially developed by a group of unrelated donor registries in Europe. EMDIS, the European Marrow Donor Information System, is used by NMDP and other international registries to exchange current information on donor search activity. At its simplest, EMDIS is a "query-response" system; where the registry initiating a search asks a question, for example, "Do you have any donors with the following HLA type?" and the responding registry answers with a listing of donor IDs and their corresponding HLA data. All of this is conducted, of course, with numbered and encrypted internet messages. The EMDIS system also allows for a much more sophisticated messaging, such as requests for confirmatory typing and the associated results, donor availability queries, donor reservations, etc.

AGNIS wants to create a similar automated data exchange for transplant outcomes data. Successfully implemented, AGNIS could be adapted to all sorts of data – cardiovascular studies, drug trials, etc. – making AGNIS truly a "growable" network solution.

AGNIS is in its early design stages, but it is already clear that it must offer several sophisticated services. These include services that insure data are not provided without permission and that data confidentiality is assured. AGNIS must track what data have been sent to various destinations as well as the origins of all the data received. It must have a system that allows for updates to data; for example, when a data audit reveals a correction, that correction should be propagated throughout all of the databases that are sharing the relevant information.

Conceptually, an AGNIS message can be envisioned as a box filled with envelopes, each envelope has a name on the outside that identifies the piece of information contained within. The name on the outside of the envelope is termed a "data element" identification. The computer sending an AGNIS message first fills each envelope with the data identified on the outside. The completed box full of envelopes is electronically sent to the receiving computer, which opens the envelopes, retrieves the data and stores them, according to the data element identification, in the corresponding fields of the receiving database. In order for such a system to work, the envelopes, that is, the data elements, must be predefined and grouped into appropriately structured messages (boxes). To complete the analogy, the outside of the box will be plastered with a great deal of additional information including recipient addresses, contents and detailed handling instructions. The attraction of AGNIS is that it is largely hardware independent, that is, the computers and databases at each end of an AGNIS communication can be conventionally incompatible. Much of the software code used to implement AGNIS is written to be platform independent, so that it can be implemented in Windows, MacOS or UNIX.

Key to the implementation of AGNIS is robust identification of transplant-related data elements and the corresponding AGNIS message structures. In order to accomplish these major tasks, the CIBMTR and NMDP have created two working committees. The first, the AGNIS Steering Committee, is comprised of international experts in transplantation and in understanding transplant data and its description. The Steering Committee's task is to describe the data elements and discuss how these data elements should be grouped and packaged. Their efforts will be implemented through the AGNIS Technical Committee, comprised of experts in information technology from the NMDP, CIBMTR and elsewhere.

A prototype system capable of transmitting rudimentary forms data between the Milwaukee campus of CIBMTR and the Minneapolis offices of the NMDP will be operational late in 2005. Persons who would like more information on AGNIS, or who would like to be kept apprised of the project status, should contact Dennis Confer at the National Marrow Donor Program (dconfer@nmdp.org) or Doug Rizzo at CIBMTR (rizzo@mcw.edu).

Continued from page 4

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Clinical Trials Network Registering and Reporting Process

The Blood and Marrow Transplant Clinical Trials Network (BMT CTN) has now been enrolling patients on trials for just over 2 years. There are currently 6 open trials with several on their way to being opened. We would like to take this time to go through the registering and reporting process for those teams that are involved in the BMT CTN.

For those teams involved with the BMT CTN, all patients, including those enrolled on a BMT CTN protocol as well as those not on a BMT CTN protocol, (both Allogeneic transplants as well as Autologous transplants) are to be registered with the CIBMTR using the Pre-Registration form. The BMT CTN is required by the NHLBI to report all transplant activity of all BMT CTN participating centers. Therefore, the CIBMTR needs all patients registered so this report will be accurate. Patients that are enrolled on a BMT CTN trial will need to be designated by a green sticker affixed to the Pre-registration form so the CIBMTR can designate the patient correctly in our database and a Report Form will be due for these patients. The green stickers are available from the EMMES Corporation at your request. For electronic Pre-Registration, please submit a list of BMT CTN patients via fax or e-mail when submitting the data. We request that the Pre-registration Forms be submitted up to two weeks prior to the start of conditioning, but we need to have them no later than 28 days posttransplant. CIBMTR is working with EMMES to keep track of how many transplants are being performed and which patients/transplants have not been registered with the CIBMTR but have been enrolled with EMMES. Please submit these Pre-Registration Forms as soon as possible.

Day 100 Report Forms (consisting of Core Insert, Graft Insert, and Disease Insert) need to be submitted to the CIBMTR within thirty (30) days of Day 100 post-transplant for all of the BMT CTN Patients. Follow-up Report Forms (consisting of the Follow-up Core Insert and the Follow-up Disease Insert) need to be submitted to the CIBMTR within thirty (30) days of the yearly visit by the patient or the patient's death date if it is between yearly Reports. If the patient received a cell product from the NMDP, then it is acceptable to submit the NMDP Form 120, NMDP Form 130, and a CIBMTR Graft Insert in the place of a CIBMTR Day 100 Report Form. Note that the NMDP Forms should only be sent after they are verified by the NMDP to the error-free.

Summary of Submission timelines for BMT CTN Enrolled Patients:

Pre-Registration Form – up to 2 weeks prior to start of conditioning, but no more than 28 days post-transplant

Day 100 Report Form – within thirty (30) days of Day 100 post-transplant

Follow-up Report Form – within thirty (30) days of the yearly visit or the date of death if between reporting times

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