Blood and Marrow TRANSPLANTATION

REVIEWS

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IN THIS ISSUE

Extending the Frontiers of Hematopoietic Cell Transplantation

John R. Wingard, MD, Editor

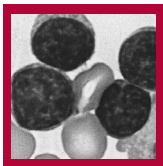
For years, considerable attention was devoted to just getting it right: figuring out how to do a transplantation as safely as possible and preventing acute complications during the first 100 days from unraveling the effort. Tremendous advances in transplantation practice have made this therapy safer and outcomes have improved. In recent years, attention has shifted increasingly to other important considerations. Questions as to how to identify who should undergo transplantation as early in their treatment as possible, how to decide between the various transplantation donor options, and how to handle the transplantation survivor no longer under the direct care of the transplantation clinician but receiving care in the community are all receiving increasing attention.

This issue contains a transcript of an educational program sponsored by the National Marrow Donor Program in December 2006 presented as a satellite symposium at the American Society of Hematology annual meeting. Dr. Forman discusses the thorny issue of identifying which patients are suitable candidates for transplantation and whose prospects for long-term survival would be best served by proceeding to transplantation as early in the course of the disease as possible. Dr. Weisdorf discusses the new option of cord blood, which already has an established role in transplantation for children and is now being extensively evaluated in adults. Dr. Lee describes the late complications that occur in survivors and strategies for screening, prevention, early intervention, and patient education. Dr. Beatty presents the community physician's perspective in referring a patient for transplantation and emphasizes the importance of 2-way communication. Dr. Rizzo emphasizes the importance of clinical trials in determining the role of transplantation in various diseases and in improving transplantation outcomes.

With continuing growth in transplantation activity and more transplantation survivors, communication between transplantation clinicians and community physicians is crucial. Also, empowering transplantation survivors to engage in health maintenance and promotion behaviors by providing information directly to them is important. The American Society for Blood and Marrow Transplantation, National Marrow Donor Program, Center for International Blood and Marrow Transplant Research, and a variety of patient advocacy groups are working to provide greater awareness to physicians and patients either singly or increasingly in partnership.

Examples include publication of guidelines for transplantation timing (www.marrow.org), evidence-based guidelines for the role of transplantation for specific diseases (www.asbmt.org), educational materials for community physicians and patients about what health problems to look for in transplantation survivors, suggested screening procedures for health maintenance (www.asbmt.org), and web sites that provide patient and family resources and expert medical advice to individual patient queries (www.bmtinfonet.org, www.bonemarrow.org, www.nbmtlink.org, and others).

The frontiers of transplantation knowledge are indeed being expanded in many different ways.



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PRELIMINARY APPLICATION

Be a part of a national organization established to promote education, research, and medical development in the field of blood and marrow transplantation.

Full Membership is open to individuals holding an MD or PhD degree with demonstrated expertise in blood and marrow transplantation as evidenced by either the publication of two papers on hematopoietic stem cell transplantation–related research as recorded by curriculum vitae, or documentation of two years of experience in clinical transplantation as recorded by curriculum vitae or letter from the director of a transplant center attesting to the experience of the candidate.

Associate Membership is open to individuals with an MD or PhD degree who otherwise do not meet the criteria for full membership.

Affiliate Membership is available to allied non-MD or non-PhD professionals who have an interest in blood and marrow transplantation. This category is especially appropriate for nursing and administrative staff of bone marrow transplant centers, collection centers, and processing laboratories, and for professional staff of corporations that provide products and services to the field of blood and marrow transplantation.

In-Training Membership is open to fellows-in-training in bone marrow transplantation programs. A letter from the transplant center director attesting to the applicant's training status is required.

Included in the membership fee is a one-year subscription to ***Biology of Blood and Marrow Transplantation*.**

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Robert Soiffer Installed as President; Claudio Anasetti Elected Vice President

Robert Soiffer, MD, chief of the Division of Hematologic Malignancies at Dana-Farber Cancer Institute and associate professor of medicine at Harvard Medical School, Boston, has been installed as president of the American Society for Blood and Marrow Transplantation.

Claudio Anasetti, MD, professor of oncology and medicine at the University of South Florida, and program leader of the Blood and Marrow Transplant Program at H. Lee Moffitt Cancer Center and Research Institute, Tampa, is the newly elected and installed vice president, to become president in 2009.

The installation of new officers and directors occurred at the society's annual meeting, the BMT Tandem Meetings, on February 10 in Keystone, Colorado. The election was by mail ballot among members of the society in December and January. Newly elected and installed directors are:

- Jeffrey Rodney Schriber, MD, of the City of Hope/Samaritan Bone Marrow Transplantation Program in Phoenix
- Paul J. Martin, MD, of the Fred Hutchinson Cancer Research Center and the University of Washington in Seattle
- Ginna G. Laport, MD, of the Division of Bone Marrow Transplantation at Stanford University in Stanford, California.

Helen Heslop, MD, was elevated to president-elect and will assume the presidency in 2008. She is professor of medicine and of pediatrics and director of adult stem cell transplantation at the Center for Cell and Gene Therapy, Baylor College of Medicine, Houston.

The new ASBMT president, Dr. Soiffer, is co-director of Hematopoietic Stem Cell Transplantation at Dana-Farber and Brigham and Women's Hospital. He also is the chair of the Pharmacy and Therapeutics Committee at Dana-Farber.

He is a member of the executive steering committee of the Bone Marrow Transplant Clinical Trials Network (BMT-CTN), and a member of three of the network's committees: toxicity, acute myeloid leukemia, and graft-versus-host disease. He is a member of the Chronic Myelogenous Leukemia Committee of the National Comprehensive Cancer Network (NCCN).

State of the Science Symposium To Be Held June 7-8 in Michigan

A State of the Science Symposium is being organized by the Blood and Marrow Transplant Clinical Trials Network (BMT-CTN).

The conference will be held June 7-8 at the University of Michigan Biomedical Science Research Building. Details and registration information can be found on the BMT-CTN Web site at ***www.bmtctn.net.***

New FACT Accreditation Standards Published

Updated requirements for accreditation of hematopoietic progenitor cells transplant facilities are contained in the newly published Third Edition of the FACT-JACIE International Standards for Cellular Therapy Product Collection, Processing and Administration.

Major updates occur at three-year intervals for the standards, which are maintained by the Foundation for the Accreditation of Cellular Therapy (FACT).

Among the significant changes in the new edition are:

- Expanded quality management standards throughout
- Compatibility with FDA and European Union directives, including core Good Tissue Practices, donor eligibility, documentation requirements and biohazard warnings
- Redefined procedure volume requirements for clinical, collection and laboratory facilities
- Expanded requirements for pediatric competencies
- Incorporation of recommendation for ISBT 128 terminology and labeling

The new third edition of the Standards is available from the FACT Accreditation Office. Telephone (402) 427-8030.

ASBMT

Symposium Report

Blood and Marrow TRANSPLANTATION REVIEWS

Posttransplantation Patient Care: Tailored Prevention and Management Strategies

Adapted from a symposium held prior to the 2006 American Society of Hematology Annual Meeting on December 8, 2006, in Orlando, Florida. This symposium was sponsored by the Medical College of Wisconsin.

MEDICAL COLLEGE OF WISCONSIN CME program

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Faculty Disclosure

Consistent with the current Accreditation Council for Continuing Medical Education policy, the provider must be able to show that everyone who is in a position to control the content of an educational activity has disclosed all relevant financial relationships. The speakers for this symposium have indicated the following possible conflicts of interest.

Dr. Dennis Confer indicated no conflicts of interest.

Dr. Stephen Forman indicated no conflicts of interest.

Dr. Daniel Weisdorf has received research support from AnorMED, Merck, Amgen, Genzyme, SuperGen, and Ligand and has received advisory board honoraria for Genzyme, Pharmion, and Schering-Plough.

Dr. Stephanie Lee indicated no conflicts of interest.

Dr. Patrick G. Beatty indicated no conflicts of interest.

Dr. J. Douglas Rizzo indicated no conflicts of interest.

Program Description

This publication will explore practical consideration for posttransplantation care in key areas, including strategies for related versus unrelated donor transplants and cord blood recipients. Using case studies, a transplanter and a nontransplanter will provide their perspectives for care once a patient leaves the transplantation center. They will discuss routine monitoring, benign signs and symptoms that should be addressed, and emergency presentation cases. The role of clinical trials will be addressed.

Learning Objectives

- Describe similarities and differences in management of related versus unrelated donor transplantation patients.
- Identify differences in postmanagement strategies for patients receiving cord blood.
- Apply long-term monitoring guidelines.
- Describe signs of serious complications.
- Discuss clinical trials in posttransplantation care.

Accreditation Statement

The Medical College of Wisconsin is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

Designation of Credit Statement

The Medical College of Wisconsin designates this educational activity for a maximum of 1.0 *AMA PRA Category 1 Credit*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

National Marrow Donor Program

The National Marrow Donor Program facilitates unrelated marrow, peripheral blood stem cell, and cord blood transplantation. The Program provides research, medical education, and patient advocacy to extend and improve lives through innovations in transplantation.

Introduction

Dennis L. Confer, MD

The use of hematopoietic cell transplantation, particularly in the unrelated donor setting, is increasing annually. At the same time, transplantation-related early mortality in the first 100 days to 1 year is decreasing. As more patients survive months and years after transplantation, aspects of patient management are changing. For the primary care physicians and the hematologist/oncologists who made the original diagnosis and referred the patients for transplantation, the need to provide longer-term care is increasing. To address this need, we present an overview of changing strategies and care practices that relate to posttransplantation care, beginning immediately after transplantation and moving forward, through long-term care and, ultimately, quality-of-life assessments.

From the inception of the National Marrow Donor Program (NMDP) in 1987, when it facilitated 2 bone marrow transplantation procedures, there has been a steady increase in transplantation treatment. From 1987 through the mid 1990s, all unrelated transplantations used bone marrow. Then, in the mid 1990s, the first peripheral blood stem cell transplantations from unrelated donors were performed. The use of this new procedure increased rapidly after 2000, so that now approximately 70% of transplantations from adult unrelated donors use peripheral blood stem cells (PBSC) and only 30% use bone marrow. Bone marrow is still preferred for pediatric patients, but for adults there has been a dramatic switch from bone marrow to PBSC even though the comparative benefits of PBSC and marrow continue to be defined.

The number of cord blood transplantations facilitated by the NMDP, which is probably about half of the cord blood transplantations performed in the United States, has also grown dramatically, actually doubling between the 2005 and 2006 October 1 through September 30 fiscal years. During this period, the transplantations facilitated by NMDP increased by 22% in just 1 year, and much of that increase was because of the growth in cord blood transplantation and the increase in the number of older transplant recipients.

Along with the dramatic increase in the number of transplantations there has been a continuous reduction in 1-year treatment-related mortality. Data from the Center for International Blood and Marrow Transplant Research (CIBMTR) combined with NMDP data show decreasing transplantation-related mortality not only for autologous transplantation, for which mortality has always been low, but also for HLA-identical sibling transplantation, alternative related transplantation, and unrelated donor transplantation. Within each area, transplantation-related mortality varies according to the type of disease and the stage of the disease. For example, there is clearly a difference in transplantation-related mortality in patients with acute myelogenous leukemia compared with patients with immune deficiencies. Some variation is probably attributable to the difference in age of recipients, but it is also due to the differing clinical characteristics of the underlying disorders. Mortality also varies within the leukemias according to the stage of the disease. Patients who undergo transplantation earlier in the course of their disease, in the first or second complete remission, do better and survive longer. Thus one of our most important messages for practicing hematologist/oncologist is to refer patients for transplantation at a time when they are most likely to received the full benefits of the procedure.

Another challenge facing those who provide health care to transplantation patients is a positive one. The increasing population of patients who achieve long-term survival through transplantation will need multi-year follow-up, during which they will be in the care of the referring hematologist/oncologist for a much longer period of time than has occurred in the past. The CIBMTR, in collaboration with the NMDP, has recently developed 2 posttransplantation guides (an autologous version and an allogeneic version) that transplantation patients and their physicians can use to track long-term follow-up care. These free guides can be downloaded from the CIBMTR web site (www.cibmtr.org/posttransplant). [Editor's note: See page 3 to preview guides.]

Planning and Management for Related and Unrelated Donor Transplantation: Day 10 to Day 100

Stephen J. Forman, MD

Transplantation requires considerable coordination involving the team identifying a donor, the team performing the transplantation, the treating physician, and the community. Important issues include awareness of the clinical situations under which allogeneic transplantation is considered for adults, differences in decision making for patients who are being considered for unrelated donor transplantation, and the similarities and differences in the care and management within the first 100 days of patients who have undergone related or unrelated donor transplantation.

Clinical Indications and Decision-Making for Adult Allogeneic Transplantation

Diseases that are treatable by related and unrelated-donor allogeneic hematopoietic transplantation include the malignant disorders of the hematopoietic and immunologic systems (Table). Timing, indications, and other aspects of transplantation differ depending on prognosis and disease characteristics at diagnosis. The decision of whether transplantation should be performed early versus at the time of relapse and progression is based on response to therapy, the nature of the disease, and the available therapeutic options. Age is no longer a barrier to transplantation; patients in their 70s have undergone successful transplantation, and the spectrum of diseases and ages for which transplantation is an option continues to expand.

Patients whose disease is responsive to chemotherapy and who go into early remission with 1 cycle of therapy are better candidates for transplantation than patients who require 2 or more cycles of therapy to achieve remission. For patients with good-risk cytogenetics who go into remission with 1 cycle of therapy, cure rates are so high that transplantation can be held as a back-up treatment, whereas for many patients with poor-risk disease, transplantation is the only potentially curative treatment. Another consideration is the duration of response. It remains difficult to determine whether a patient who relapses after primary therapy will have a better outcome with repeat chemotherapy or transplantation. For relapsed acute myelogenous or lymphocytic leukemia (AML or ALL), reinduction chemotherapy options are limited and transplantation is likely to be used after relapse, but for relapsed low-grade lymphoma, 2 or 3 or more courses of treatment may be tried before transplantation.

Another important consideration is that optimal safety and efficacy of an unrelated

Diseases Treatable by Related and Unrelated Allogeneic Donor Transplantation

Acute myelogenous leukemia
Acute lymphocytic leukemia
Myeloproliferative disease/myelofibrosis
Myelodysplastic syndrome
Multiple myeloma
B-cell lymphoma (low grade, mantle cell, large cell)
Chronic myelogenous leukemia
Chronic lymphocytic leukemia
Aplastic anemia

donor transplantation occur when the alleles of the donor and recipient are matched. HapLogic and other advanced NMDP informatics tools have been developed so that an allele-level match can sometimes be identified in an unrelated donor as quickly as in a related donor. Molecular matching of an unrelated donor and recipient narrows the difference in outcome, so proceeding with early transplantation is an option for patients who do not have a sibling donor but have a molecularly matched unrelated donor.

Although allele-level matching can now be performed for related and unrelated patients undergoing transplantation, there may not be an allele-matched donor available, and for patients with rare alleles a perfectly matched donor frequently cannot be identified. The potential gain of extending the donor search to find a fully compatible donor must be weighed against the harm of lengthening the time from diagnosis to transplantation.

Risk categories can be useful for determining whether to accept the risk for some degree of imperfect matching, and disease status can determine how long to wait for an ideal donor. For low-risk patients for whom transplantation is most likely to be curative, such as patients with chronic myelogenous leukemia (CML) and low-grade lymphoma, results with allele-level donor matching approximate those achieved with a sibling donor. Thus waiting for a good match to proceed with transplantation may improve outcomes for low-risk patients, provided their disease does not progress during the delay. Disease control outweighs allele-level matching, however, for intermediate-risk patients (those with more advanced disease such as CML who undergo transplantation more than 2 years after diagnosis or have AML in remission or myelodysplastic syndrome [MDS]) and high-risk patients (those in relapse or with more advanced MDS with blasts or poor-risk cytogenetics).

Patients for whom allogeneic transplantation should be considered early include patients with AML or ALL who do not go into remission in the first 1 or 2 cycles of chemotherapy and patients for whom transplantation offers the only possibility of cure and can be successful in 20% to 40% of patients. Patients with CML resistant to kinase inhibitors such as imatinib mesylate are curable by transplantation [1]. MDS with increased blasts or with poor-risk cytogenetics and AML with poor risk cytogenetics generally are curable only by transplantation. Other diseases for which early transplantation should be considered are myelofibrosis, low-grade lymphoma with a short remission after chemoimmunotherapy, and chronic lymphocytic leukemia (CLL) refractory to fludarabine.

Care of Patients Undergoing Related or Unrelated Donor Transplantation

Donor Identification and Selection

For all patients, even if transplantation is not considered an immediate option, HLA typing and the assessment of the possibility of either a related- or unrelated-donor transplantation should be part of the initial evaluation. Because the process of finding a donor can take several months, knowing the family or the unrelated donor situation early in the course of the disease allows better planning for patient care.

Preparative Regimen

The choice of pretransplantation regimen is affected by patient disease status and age. Patients with advanced disease are more likely to be managed with a full-intensity regimen, whereas older patients with a disease that is under control are often managed with a reduced-intensity regimen. With reduced-intensity transplantation, patients in their 60s and early 70s are potential candidates for transplantation. Also factored into this equation is the curative potential of transplantation, which is based in part on the specific disease. A significant component of the curative effect of all transplants is the graft-versus-leukemia (GVL) effect, but GVL sensitivity varies. Some diseases, such as CML, CLL, and low-grade lymphoma, are dramatically sensitive, and the GVL effect may still be curative with a reduced-intensity regimen, whereas ALL is least sensitive, and the role of GVL in the disease cure is less clear.

Posttransplantation Patient Care

Graft-versus-Host Disease

Graft-versus-host disease (GVHD) treatment is related to the stem-cell source and degree of mismatch. Immune suppression regimens differ for patients with a perfectly matched sibling or unrelated donors and those with mismatched donors. Corticosteroids are the best GVHD therapy but are not optimal, and studies are underway to find alternatives that offer a more complete and durable response for patients with significant GVHD. Other current treatment options include rabbit antithymocyte globulin and T-cell depletion. Patients who have acute GVHD during the first 100 days are more likely to have chronic GVHD and therefore are more likely to have later problems that must be addressed by their primary care physician.

Mucositis, which is a primary source of patient discomfort in the early posttransplantation period, is related to the preparative regimen and GVHD prophylaxis, particularly radiation-based regimens with etoposide and GVHD prophylaxis with methotrexate. Efforts are ongoing to find novel GVHD prevention regimens that will eliminate the need for methotrexate.

Infections

Reactivation of latent herpes simplex virus in the oral or genital area is common, so all seropositive patients should receive early posttransplantation prophylaxis until they are no longer on immunosuppressive medication. Herpes zoster reactivation occurs in 40% of allogeneic transplant recipients. Acyclovir, which most transplant recipients receive for 1 year, is fairly effective in preventing reactivation, but after 1 year reactivation may still occur when the acyclovir therapy is stopped. Because herpes zoster vaccine is a live virus, it is not appropriate for patients on immunosuppressive drugs.

Most cytomegalovirus (CMV) reactivation occurs between day 20 and day 80 posttransplantation. CMV was once the cause of death before day 100 in 20% of transplantation patients, but now because of pre-emptive strategies, death from CMV in the first 100 days is rare. All transplantation programs screen for the virus and treat with oral or intravenous ganciclovir for positive culture or polymerase chain reaction rather than waiting for overt disease. New, more effective means of CMV control include new drugs and donor

immunization with CMV as a way of transferring to the recipient an immune system that is more likely to control CMV. If CMV is detected during the first 100 days posttransplantation, even if it is successfully treated, the patient needs ongoing monitoring for possible late reactivation.

Bacterial infections are related to the extent and duration of neutropenia. Hospitalized patients must be monitored for methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *enterococcus*. All patients are screened for *Clostridium difficile* before transplantation, but *C difficile* should be ruled out if a patient develops diarrhea after transplantation.

All patients require fungal prophylaxis. Risk factors for fungal infection include neutropenia and steroid use. Pneumocystis prophylaxis is needed by all patients in the early posttransplantation period and must continue as long as the patient is on immunosuppressive therapy. Physicians need to be aware that antifungal drugs may interact with immunosuppressive drugs.

Case Presentations Highlighting Pretransplantation Management

Relapsed AML

The first patient illustrates circumstances commonly encountered in patients by physicians and transplantation centers. A 37-year old male patient with FAB AML with normal cytogenetics, a disease category that has neither a good nor poor risk, responded to treatment and went into remission after 1 month of induction therapy and then received 3 months of consolidation therapy. Approximately 6 months later, the patient developed thrombocytopenia with leukemic relapse and was referred for evaluation for allogeneic transplantation.

Because the cure rate for normal cytogenetic AML is, at best, 35% to 40%, the patient's family should be tissue typed at diagnosis and a search for an unrelated donor should be performed. If a suitable donor is found, the decision must be made either to perform reinduction therapy or go directly to transplantation. Factors affecting this decision are how quickly transplantation can be performed, the duration of first remission, and the tumor burden. For patients who relapse within 1 or 2 months after achieving a remission, the rate of second remission is approximately 50%. Thus this patient, who relapsed within a few months, is unlikely to go back into remission, so unless he has the option to participate in an investigational trial, if the tumor burden is relatively low and a suitable donor is available, the best treatment option is transplantation without a reinduction attempt with an intensive pretransplantation regimen. Under these circumstances, the patient has a 40% to 50% chance of cure. With a high tumor burden, for example a white count of 100,000 with relapse, reinduction therapy is needed to attain better disease control before transplantation even if a suitable donor is available. If a donor is not yet available, reinduction with an investigational or other agent should be initiated while the donor search is ongoing.

Fludarabine Refractory B-Cell CLL

This patient is a 47-year-old man with B-cell CLL diagnosed 8 years earlier. Over the course of the next several years the disease progressed, and the patient began treatment with a fludarabine/rituxan regimen with a good response for approximately 2 years, but eventually his disease became refractory to fludarabine treatment. Most CLL patients do well with a fludarabine-based regimen, but patients who have a very short response or no response should be tissue typed and assessed for donor availability. Fludarabine-refractory CLL, as seen in this patient, is a disease for which the GVL effect is probably the strongest component of the transplantation regimen. A striking feature of transplantation for CLL is that the disease will still be present on day 30. The GVL effect is there, but it develops over time.

Secondary MDS

The third patient is a 55-year-old woman with MDS secondary to chemotherapy for breast cancer and without a related donor. This is an example of a patient for whom only recently transplantation may have been impossible but is now an option because new epigenetic-based therapies that affect methylation or acetylation to allow better disease management. After treatment with the epigenetic agent azacytidine and identification of an unrelated donor, this patent was able to undergo transplantation. So for secondary versus primary MDS, with poor outcome related to disease, if a sibling-matched donor is available then immediate transplantation is indicated; if no sibling donor is available, epigenetic therapy should be initiated, and then transplantation should be performed if an unrelated donor is found.

Conclusions

Allele-level matching narrows the differences in outcome between related and unrelated donor transplantation in patients with lower-risk disease and allows a physician to consider matched unrelated transplantation earlier in the course of disease. Age is no longer a barrier, and the management principles are exactly the same for older and younger patients. Long-term follow-up requires close communication among the transplantation team, the physician, and the patient and family, beginning at diagnosis. The process of finding a suitable donor should begin even before transplantation is considered as an immediate treatment option so that the patient and physicians can explore available options and time the transplantation based on the biology of the disease.

Reference

1. Holtz M, Forman SJ, Bhatia R. Growth factor stimulation reduces residual quiescent chronic myelogenous leukemia progenitors remaining after imatinib treatment. *Cancer Res.* 2007;67:1113-1120.

Unique Considerations for Patients Receiving Cord Blood Transplants

Daniel Weisdorf, MD

The field of umbilical cord blood transplantation (UCBT) is still in its infancy, and we are still trying to understand how UCBT differs from other forms of transplantation. Biological features of UCB cells suggest they might be suitable and perhaps even better as sources of hematopoietic cells for transplantation. UCB hematopoietic stem cells are highly proliferative, and this rapid proliferation can overcome the limited cell dose available in a single-cord unit. Because these cells have a naïve immune system, recipients may have satisfactory outcomes with partially matched transplantation, thus extending the donor pool to ethnic and racial minority groups for whom finding allele-matched adult donors can be difficult, if not impossible. Another advantage is that the supply of UCB cells is unlimited, because every baby born is a potential donor. UCB units that have been characterized, typed, and screened for infectious disease markers can be frozen and stored and then shipped rapidly to a transplantation center.

Data on long-term outcomes are not currently available for sufficient numbers of UCBT recipients. To date, however, matched-pair analyses have shown similar survival rates for patients, primarily children, who received partially matched UCBT and those who received reasonably well-matched unrelated donor transplants [1]. On the basis of these results, UCBT is now a standard option for the management of pediatric patients, particularly those with pediatric leukemia.

Cell Dose and UCBT Outcomes

Experience with UCBT has revealed that the cell dose is critical. An analysis of neutrophil engraftment in approximately 100 UCBT showed that patients who received <1.7 x 107 cells/kg of recipient weight had slow, incomplete neutrophil recovery that led to high transplantation-related mortality [2]. These results suggest that 2 x 10^7 cells/kg might be the minimum cell dose for a satisfactory graft (Figure 1), but further validation is needed.

Other Factors Affecting UCBT Outcomes

Although we can overcome some HLA barriers with UCB, matching is still important. It is not yet clear, however, how to balance matching with cell dose. The greater the number of recipient-donor mismatches, the greater the rate of adverse events. Some evidence suggests that a larger cell dose can compensate for a greater mismatch, whereas a smaller dose may lead to better outcomes for closely matched cord blood. Even with a satisfactorily sized cord blood unit, graft failure is a possibility with UCBT and requires consideration and planning ahead of time. The risk of graft failure increases in adults as compared to children, probably because of increased body size.

Data comparing outcomes of cord blood grafting versus unrelated donor bone marrow [3] indicated that neutrophil recovery was slower and less complete in adults receiving UCBT than in those who received either matched or partially matched unrelated donor bone marrow. Newer data, however, suggest that outcomes may be improving. A more recent published study [4] showed that platelet recovery in cord blood recipients is less rapid than in bone marrow transplant recipients, but cord blood leads less often to graft failure than it did in the early phase. The rate of graft failure with unrelated UCBT has been 20% to 30% overall, with an additional risk of late graft failure. With the current understanding that grafts must contain a sizable cell dose (2 to 5 x 10^7 cells/kg), the rate of graft failure is 5% to 10%.

Graft Failure in UCBT

Because graft failure occurs in as many as 5% or 10% of UCBT patients even with a well-matched, suitably sized cord blood unit, it is important to anticipate the need for backup grafts. Along with choosing the primary graft to be used for the transplantation, the availability of suitable backup grafts, either cord blood or unrelated donor, should be assessed. Patients should be monitored for evidence of recovery of donor hematopoiesis; if this does not occur by day 35, a second graft should be requested and immunosuppressive conditioning initiated. As many as 50% of patients who have graft failure can be rescued by a planned approach initiated before day 50 posttransplantation, when the patient may have persisting neutropenia and mycotic infection.

Double-unit UCBT with 2 closely and suitably matched cord bloods may provide better engraftment because each unit is an independent immune system; they will not reject each other, and by providing a bigger and more effective graft to adult patients their use may lead to improved recovery and survival (Figure 2). Double-unit UCBT is not chosen preferentially over single UCBT but offers an option for patients for whom no satisfactorily sized single-cord graft is available. In these patients, adding the second unit leads to successful engraftment in almost 90% of cases.

A surprising finding with this procedure is that recipients of double-unit UCBT had lower rates of relapse than single UCBT recipients. In 109 patients with acute leukemia in first or second remission, the difference in relapse rates was statistically significant, a finding suggesting that doubling the UCB units has an important immunological effect that might lead to reduction in relapse.

Although the problem of limited cell dose, which compromises early outcomes, might be overcome by double-unit UCBT, many adults who undergo this procedure have advanced-stage disease, have undergone extensive prior therapy, or have poor fitness, all of which may lead to a high treatment-related mortality rate independent of cell dose. The use of a reduced-intensity non-myeloablative conditioning regimen in such patients has led to higher rates of successful engraftment with single- and double-unit UCBT. The transplantation-related mortality rate with this non-ablative approach was only 18% at 6 months, and the 3-year survival rate is approximately 44%, suggesting that UCBT may be an effective option for adults who are too old or too sick for conventional myeloablative approaches.

With both myeloablative and reduced-intensity or non-myeloablative transplantation, rates of acute graft-versus-host disease (GVHD) are higher in UCBT patients than in patients with grafts from other sources, approximately 40% with single-unit UCBT and 66% with double-unit UCBT. This higher rate of GVHD does not completely explain the decreased risk of relapse. Research is ongoing to investigate the possible association of the graft-versus-leukemia potency of double-unit UCBT with modest or more serious GVHD. Comparison of chronic GVHD in UCBT and unrelated-donor transplant recipients has shown that in UCBT recipients, chronic GVHD seemed more responsive to immunosuppressive therapy, leading to lower non-relapse mortality at 1 year.

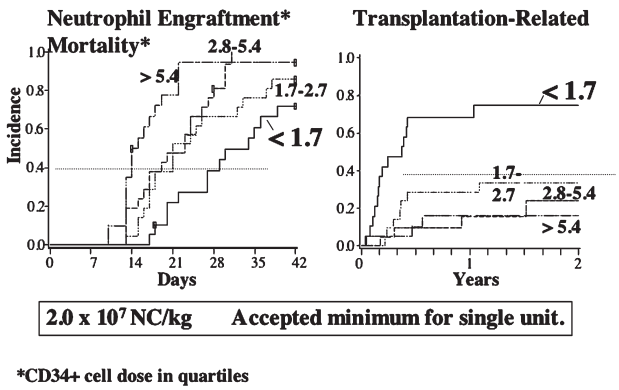

Figure 1. Minimum cell dose for umbilical cord blood transplantation.

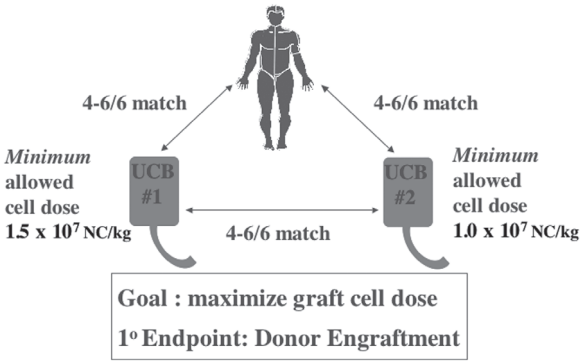

Figure 2. Double-unit umbilical cord blood transplantation.

It has been postulated that UCB recipients may be at higher risk of ongoing late infections, but across the whole spectrum of types of infections, higher infection rates have not been observed. Data on infections after adult UCBT compared to either peripheral blood or bone marrow transplantation showed that serious infection rates were a little higher after cord blood, but infection-related mortality was similar at 100 days. CMV disease rates were similar in the 2 groups, although the CMV infections appeared earlier after UCBT, possibly because UCB donor grafts are CMV seronegative and CMV naïve, therefore not providing any effective T-cell protection against CMV reactivation, but the overall risk was not different. The bacterial infection rate was somewhat higher in UCB recipients, but the fungal infection rates were similar in the 2 populations. Thus, evidence to date does not indicate that UCBT leads to more frequent infections.

Conclusions

UCBT studies reflect a dramatic learning curve from the late 1990s to current experience. Reports of outcomes of early grafts, particularly for adults, that were done with too small a graft probably do not contribute to an understanding of what can be expected now that we know how large a cord blood unit should be to achieve satisfactory outcomes.

UCBT is associated with more graft failure. Because graft failure can be anticipated to occur in 5% to 10% of patients, it must be planned for ahead of time. Excess acute or chronic GVHD does not seem to occur with UCBT. Double-unit UCBT, although it improves engraftment, leads to more frequent acute GVHD but not more frequent transplantation-associated mortality or more frequent chronic GVHD. UCBT does not seem to be associated with a greater frequency in early or late infections, but the quality and functional capacity of the immune system after UCBT has yet to be been evaluated.

Double-unit UCBT appears to have potent graft-versus-malignancy effects, manifested by the lower relapse rates after 2 versus 1 UCB grafts, an effect that is being investigated in a prospective pediatric trial. Overall, published reports indicate that survival after UCBT is similar, and for some selected populations may be superior, to that with unrelated donor transplantation. More experience is needed to move the field of cord blood transplantation beyond its infancy.

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Routine Long-term Follow-up of Hematopoietic Cell Transplantation Survivors

Stephanie Lee, MD, MPH

Late non-relapse mortality is a tragic outcome of otherwise successful transplantation, and long-term transplantation survivors suffer substantial morbidity from chronic graft-versus-host disease (GVHD) and treatment-related effects. Whether optimal medical care can prevent these late effects is not known, but it is reasonable to assume that good medical care can minimize their impact and, conversely, poor medical care can probably exacerbate them.

Optimizing Long-term Posttransplantation Follow-up

Five concepts underlie the optimal approach to routine follow-up. The first is clearly the prevention of complications that can be avoided in at-risk patients. For complications that cannot be prevented, screening is important because in most cases early detection increases the likelihood of successful treatment. For existing complications, appropriate intervention is essential. Patient education is also very important so that patients will be involved in their own care and report symptoms that occur between visits. Finally, serious problems must be rapidly identified so that appropriate interventions can be initiated.

The need for infection prophylaxis and vaccinations is a familiar aspect of preventive care of posttransplantation patients. Good dental hygiene and minimization of sun exposure are also important strategies because transplantation patients are at a higher risk for dental caries and oral cancer, and sun exposure can exacerbate chronic GVHD and increase the already higher risk of posttransplantation skin cancers. Even before transplantation, conditioning regimens can be selected that minimize the risk of late complications. Another preventive strategy is fertility preservation, which often requires pretransplantation procedures such as sperm or embryo cryopreservation.

Screening and early detection involve screening for cancer recurrence and late effects of treatment, but general health screening is also important. In the general population, internists often do such screenings, but

for transplantation patients, oncologists or transplantation physicians may assume the role of the primary care provider.

Posttransplantation care can be provided through 2 types of follow-up visits. Routine interval visits involve history and physical exams to assess for the presence of new signs and symptoms, routine diagnostic studies, and review of medications. Time-dependent evaluations involve checking all the systems for early signs of any problems and include regularly scheduled vaccinations, dental and eye exams, and screening procedures for new and old cancers. Such evaluations, often scheduled on the basis of time from transplantation and patient age, include assessments of endocrine function, thyroid function, and bone health.

Long-term follow-up involves every organ system because for each system there is at least one potential catastrophic event that requires surveillance. Secondary malignancies are associated with chronic GVHD or the conditioning regimen. Non-melanoma skin cancer, squamous cell and basal cell, is the most common secondary malignancy. The rates for solid tumors in posttransplantation patients are 2.2% at 10 years and 6.7% at 15 years. In 5-year survivors, cancer risks compared with the general population are highest for bone, oral, connective tissue, liver, brain, and thyroid cancer and melanoma. Breast cancer becomes more common in 10-year survivors. Most of these cancers are unusual and lack effective screening approaches. Thus it is important that follow-up exams include careful skin and mouth exams, feeling the thyroid for nodules, and checking the mammogram in women.

Items to be addressed in a comprehensive 1-year long-term follow-up visit are presented in the Table. The goal is to maintain patient health and to use the opportunity, given the fact that the patient sees medical practitioners frequently and has had a brush with death, to provide more attention to health and better health care maintenance afterwards. In addition to surveillance for secondary malignancies, screening tests that are appropriate for the general population also apply to transplantation patients. Colorectal cancer screening is recommended at age 50, or sooner if there is a family history. For breast cancer, regular mammograms every 1 to 2 years are recommended to begin at age 40 or 50, but should begin earlier in women who have had radiation therapy. Regular PAP smears for cervical cancer should begin at age 21 or the onset of sexual activity. For prostate cancer screening there is no consensus, with some organizations recommending fairly extensive workup including prostate-specific antigen and digital rectal exam, and others saying that data do not support these procedures.

In long-term survivors the most common cause of death is cardiovascular disease. Recommendations are to check blood pressure every year and to treat it if it is consistently over 140/90. Lipids, cholesterol, and high-density lipoproteins should be checked every 5 years starting at age 35 for men and age 45 for women. Screening for diabetes is also recommended.

Patient care can be enhanced by cooperation between the oncologist or transplantation physician and other physicians such as an internist who can help with cancer screening, cardiovascular risk factors, and bone health and a dentist who can help with oral cancer screening. Written materials can also facilitate clinical care. These may include patient self-assessment, screening questions, and lists of recommended tests based on time since transplantation. Materials available for patients participating in their own long-term care include the National Marrow Donor Program's "Living Now" pamphlets, which include information about specific topics, including medications, signs and symptoms of chronic GVHD, family relationships, and going back to work. Patient involvement is important because patients and families are the most invested in maintaining the best possible long-term health. Patient empowerment is associated with improved satisfaction and outcomes.

Components of a 1-year Follow-up Visit

Complete blood count with differential, chemistry panel (liver function tests, glucose, creatinine)
Immunoglobulin levels
Fasting lipid panel
Virology screen (hepatitis, cytomegalovirus)
Immunization titers
Endocrine evaluation: thyroid, sex hormones
Iron studies
Immunosuppressive drug levels
Bone marrow aspirate
Skin biopsy
Pulmonary function tests
Schirmer test
Dual energy x-ray absortiometry to assess bone density
Chest x-ray
Eye and dental exam
Gynecological exam/mammogram (women)
Prostate-specific antigen (men)

Conclusions

Long-term follow-up of transplant survivors involves prevention, screening, appropriate interventions, patient education, and rapid identification and treatment of serious conditions. More and more resources are available to help manage the multitude of tasks and enable patients to become better partners in maintaining their health. What we really want to do is bring the survival curve for transplantation patients up to that of the general population. To achieve this, health care providers must be vigilant for complications and think long-term about conditions that have nothing to do with transplantation but can still affect a patient's health. Ultimately, making transplantation a success involves trying to prevent patient death from something other than the original disease and its treatment.

Long-term Care of the Bone Marrow Transplantation Patient: The Referring Doctor's Perspective

Patrick G. Beatty, MD, PhD

Tension exists between transplantation physicians and the physicians who are involved in the care of patients before and after transplantation but did not perform the actual transplantation. The information provided here is meant to enable transplantation physicians to understand the perspective of the referring physician. Most important is the recognition that transplantation patients make up a very small percentage of patients seen at a busy hematology/oncology practice. Another consideration is that the referring doctor's relationship with the patients and their families can be disrupted by the transplantation process. And finally, referring doctors tend to remember the bad outcomes, so transplantation physicians can play an important role in renewing hope and optimism.

Accessing Patient Outcome Data

Referring hematology/oncology practices do not routinely track patient outcomes for their own use, particularly for transplantation patients, but they tend to remember the outcomes that

were bad. Thus the referring physician's perspective regarding transplantation tends to be colored by memories of the most heart-wrenching experiences, whereas patients who did well or are doing well do not come to mind immediately. A possible remedy for this situation may be for transplantation programs themselves to provide detailed outcome summaries to the referring physicians. Many programs send out survival curves, but these may not seem relevant to referring doctors, who may need more detailed information about the patients that have come out of their particular practice.

Referring physicians have different relationships with their patients than the academic center. They know the patients and the families very well and have a community status, which causes the families to view these physicians as sources of information. Thus these doctors would benefit from frequent outcome updates through brief communications, possibly in the form of physician-to-physician conferences. Communication regarding adverse events is essential because as soon as something goes wrong at the academic center or transplantation program, the families will start calling the referring physician for information. If the referring physician has no knowledge of the complication, it becomes a very awkward and difficult situation.

On the business side, the care of transplantation patients takes a particularly large amount of time for which the referring practice is not reimbursed, so these patients frequently entail expenses that outweigh the revenue they generate. Posttransplantation patients must take many medicines that frequently are not routinely available in the community. They may be the only person in the community who has ever taken a certain drug, the pharmacy may never have heard of it, and when they research the drug the pharmacists may not understand why the patient is taking it. Thus community physicians need more information and time to get these drugs into the pharmacy. Reimbursement for these drugs and for treatment may also becomes a difficult issue. If the patient reaches a lifetime insurance maximum, it is frequently the referring practice that must cope with a patient who no longer has the ability to pay for care.

Requests to provide follow-up data can also create difficulties for referring practices. Understanding complicated transplantation cases requires complicated data, and private practices may have limited data management capabilities. In particular, private practices do not have a system that provides funding support for data collection and data management. Frequently the doctors end up filling out the forms, if they are filled out at all, because only the doctors with enough familiarity with these complicated issues are able to fill out the forms. Easing the data-reporting burden is a huge challenge, however. New legislation in the United States requires transplantation centers to report outcomes, including long-term outcomes, on all of their allogeneic transplantation patients, so every transplantation patient who comes back to the practice will have at least some requests for follow-up data on an annual basis.

Referring physicians would benefit from being able to directly contact someone who understands what is going on and can give some advice. Frequently the doctor who referred the patient is not the same as the doctor who is taking care of the patient posttransplantation, who may be the family physician who sent them to the hematologist/oncologist in the first place.

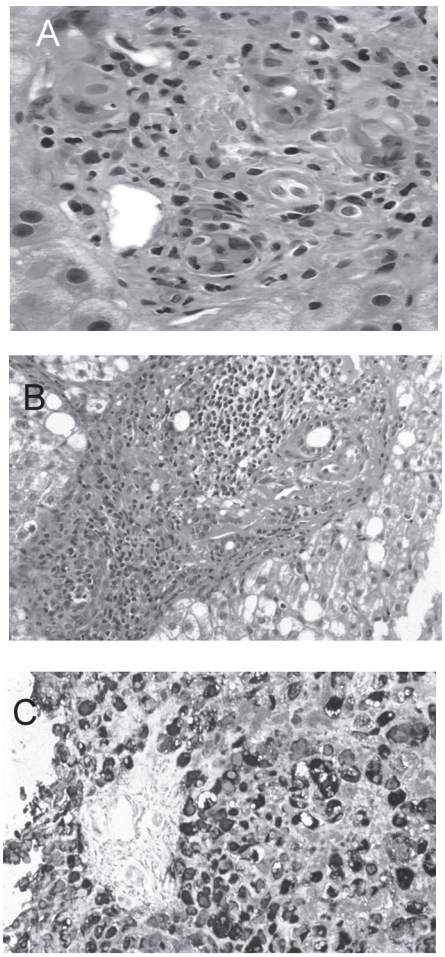
Management of Posttransplantation Complications

Long-term adverse outcomes of transplantation that are familiar to transplantation physicians may be perplexing to the referring practice. Images and biopsy specimens may be difficult for the pathologist in the referring community to interpret and frequently must be sent to the transplantation center to be examined by someone who is familiar with the complications that can be encountered with transplantation.

With respect to cytomegalovirus, patients may come back with instructions to do cytomegalovirus monitoring. If samples must be sent to a laboratory for analysis, however, results may not come back in a timely fashion, a problem that does not occur at transplantation centers but that transplantation physicians should be aware of.

Diagnosis of fungal infections is very important because effective therapies are available that can be managed in the referring practice. Most practices have experience managing pneumocystis and bacterial infections in patients with AIDS or leukemia and lymphomas in the nontransplantation setting and will have the awareness and skill to diagnose and manage these complications in posttransplantation patients.

Differentiating complications caused by graft-versus-host disease from infectious complications is essential for planning appropriate treatment. For example, when liver enzyme monitoring indicates disease, graft-versus-host disease of the liver is commonly suspected, but viruses, particularly hepatitis C and B, may be the cause (Figure). It is important to keep those infections in the differential diagnosis because the therapy is dramatically different. Differential diagnosis of gastrointestinal disorders in posttransplantation patients is also difficult because *Clostridium difficile* and other infections can mimic graft-versus-host disease. Screening pulmonary function tests are important and may require assistance from the transplantation team because abnormalities may be detectable only



Differential diagnosis of posttransplantation liver disease. A, Graft-versus-host disease (GVHD) of the liver. B, Chronic hepatitis C virus infection after allogeneic hematopoietic cell transplantation (HCT). Arrows indicate normal small bile ducts, which rule out liver GVHD. C, Fulminant hepatitis B after HCT.

with high-resolution computed tomographic scanning, which may not be readily available in the immediate community.

Disease Relapse

From the perspective of the referring physician, relapse is the most devastating of all outcomes. Patient hopes are now dashed and the promise of the transplantation has to be re-evaluated by the patient and family. Inevitably the question arises as to whether all of the difficulty in getting through the transplantation was worth it. The questions that the referring physician faces involve the possible role of re-induction, donor lymphocyte infusions, and potential retransplantation options, decisions that require input from the transplantation team.

Conclusions

Transplantation physicians who understand the difficulties faced by referring physicians can do much to improve the situation and thus optimize the long-term care of their patients. The patients who have relapsed are etched in the minds of the local practitioners, who hate to see relapse happen. When relapse does occur, the transplantation physicians can provide support and advice to ease the difficulty of providing ongoing treatment. With ongoing treatment advances, the transplantation physicians and centers may also provide continued hope.

[This report was presented at the symposium by Dr. Confer on behalf of Dr. Beatty.]

Clinical Trials: Past Trials and Current and Future Needs

J. Douglas Rizzo, MD, MS

Clinical trials help to advance patient care. Many current care practices, particularly in the early posttransplantation period, are supported by randomized clinical trials, and gaps in our knowledge that hinder the delivery of optimum care might be addressed by current or future clinical trials. In the hematopoietic transplantation setting, where the numbers of patients are limited, clinical trials are difficult to do and require cooperation between transplantation physicians and nontransplantation practitioners in both academic and non-academic settings to enroll patients in well-designed clinical trials that can help us advance our clinical practice.

Well-run clinical trials require substantial funding to support the costs associated with developing protocols, enrolling patients, collecting data, monitoring safety, and analyzing results. In addition, patient accrual presents a particular challenge in clinical trials in the hematopoietic cell transplantation setting. Each year, a few patients undergo hematopoietic cell transplantation. Because these patients are heterogeneous in regard to disease, disease stage, age, type of donor and graft, and transplantation technique, very few are eligible for clinical trials at any but the largest transplantation centers. Patient accrual for clinical trials of long-term posttransplantation care is even more difficult than for the early posttransplantation period. Physicians who care for posttransplantation patients in the community must become more active in patient recruitment for vitally needed clinical research in this area.

Designing Clinical Trials

Prospective clinical trials provide the best evidence for improving clinical practice because the experimental design and the approach to supportive care are very well defined. The data to be collected and the definitions for the endpoints are pre-specified to avoid bias on the part of the physicians who enroll and follow the patients. Randomized control groups can eliminate selection bias and allow for comparable groups across the study arms.

The Blood and Marrow Transplant Clinical Trials Network (BMT-CTN) was established in 2001 to conduct scientifically meritorious multi-center trials in an efficient manner (Table 1). The BMT-CTN seeks to improve transplantation outcomes by providing a durable infrastructure to serve as a platform for developing and evaluating promising therapies in high-quality multi-center studies that give definitive answers as quickly as possible. Areas of research include the expansion of donor availability and graft sources, reductions in transplantation-related regimen toxicity, improvement in the prevention and treatment of graft-versus-host disease (GVHD), improvement in the treatment and prevention of infection, better ways to control and prevent relapse, improvement of late immune reconstitution, and prevention of late adverse events after transplantation.

Changes in Practice through Clinical Trials

Many supportive care practices in use today have been derived from results of clinical trials performed over the last 20 years, and ongoing trials will continue to be a major factor in ongoing advances in patient care. Three areas that have been a focus of clinical research in transplantation patients are infection, GVHD, and regimen-related toxicity.

Infections are a major cause of morbidity and mortality after transplantation, accounting for at least 20% of deaths. In particular, long-term immunosuppression leads to high risk for infection. Infections that pose the greatest risk include invasive fungal infections. Clinical trials performed in the early 1990s demonstrated that fluconazole prophylaxis prevented fungal infections, with continued survival benefit and decreased GVHD of the gut at 8 years posttransplantation. The emergence of resistant species and breakthrough infections with more aggressive species such as aspergillus and zygomicides are ongoing problems that ongoing and future studies will help to address. A randomized trial comparing micafungin, an echinocandin with broader antifungal coverage, and fluconazole was published in 2004. This study found micafungin statistically superior to fluconazole in preventing fungal infection after hematopoietic cell transplantation. Patients who received prophylaxis with micafungin experienced fewer breakthrough infections with aspergillus species; however, this difference was not statistically significant.

A current BMT-CTN study is addressing the issues of resistant and emerging species by comparing fluconazole with voriconazole, which some centers currently use as fungal prophylaxis even though its effectiveness has not yet been proven in a randomized clinical trial. This study, with a targeted accrual of 600 patients at 35 sites, has the primary endpoint of survival free from probable or proven invasive fungal infection and secondary endpoints of incidence of invasive fungal infections, duration of antifungal therapy, and incidence of acute and chronic GVHD. The results of this trial, which should be available in a year, may help guide both early and later fungal prophylaxis.

Reducing the risk of azole-resistant species and the emergence of more aggressive species remains a high priority. Depending on the results of the voriconazole trial, a trial comparing micafungin with voriconazole may be very relevant in the next few years. New therapies such as posaconazole and a future generation of antifungals are also likely to lead to more clinical trials. The development of pre-emptive diagnostic testing, which may allow us to limit

Table 1. Blood and Marrow Transplant Clinical Trials Network, Established in November 2001

Mission
- Conduct scientifically meritorious multicenter trials in an efficient manner to improve transplant outcomes
- Provide the infrastructure to allow promising therapies to be developed/evaluated in high-quality multicenter studies that give definitive answers as rapidly as possible

Major Areas to be Addressed
Expansion of donor availability and alternative graft sources
- Reduction in regimen-related toxicity
- Improved prevention and treatment of graft-versus-host disease
- Improved control of malignancy (decreased recurrence)
- Better prevention and treatment of infection
- Better prevention and treatment of late effects, including better immune reconstitution

Current Clinical Trials Network clinical trials include:
- Voriconazole Fungal Prophylaxis
- Graft-versus-Host Disease Prophylaxis
- Graft-versus-Host Disease Treatment
- Therapy for Idiopathic Pneumonia Syndrome

antifungal agent exposure to those patients who are at the highest risk, and improved understanding of patient immune recovery and testing for donor innate immune response, an ancillary study in the current voriconazole trial, may allow us to further refine fungal therapy.

Viral infections also pose a substantial risk for transplant recipients. Risk is highest in the early posttransplantation period but continues in the long term for any patient who remains on immunosuppressant therapy. Reduced incidence of cytomegalovirus (CMV) mortality can be attributed to recent treatment advances. Two different approaches are prophylaxis, with the antiviral drug ganciclovir given to all seropositive patients, and early diagnosis and initiation of pre-emptive therapy at the time of detection. Clinical trials in the early 1990s showed decreased risk of tissue-invasive CMV infection in transplant recipients treated with prophylactic ganciclovir compared with placebo. Prophylaxis with oral valacyclovir seems to be more effective than acyclovir, and initial prevention with acyclovir followed either by valacyclovir or intravenous ganciclovir seems to give equivalent results. Ganciclovir is associated with a risk of myelosuppression, and pre-emptive therapy allows for initiation and discontinuation of the drug based on sensitive detection strategies. Culture-based early detection followed by ganciclovir is more effective than placebo, and polymerase chain reaction-guided detection methods seem to be more sensitive than culture techniques. Patients treated with pre-emptive therapy based on antigenemia results seem to have an increased risk of CMV invasive disease within the first 100 days after transplantation compared to those treated with prophylactic ganciclovir. After day 100, however, the risk is no different; survival is similar with both strategies, and patients in the antigenemia-guided group have a decreased risk of fungal infection.

Once antigenemia has been detected, treatment results with foscarnet appear to be equivalent to those with ganciclovir. Both prophylactic and pre-emptive strategies are currently in use, although pre-emptive strategies are more prevalent in transplantation centers.

The oral prodrug of ganciclovir, valganciclovir, may yield higher bloodstream drug levels than intravenous ganciclovir. This approach requires caution, however, because many patients with CMV also have co-existing GVHD, which may affect drug absorption when it involves the gastrointestinal tract [1].

No known prophylaxis exists for some viral infections that are common and occasionally devastating in transplant recipients (Table 2). Future clinical trials may focus on new antiviral agents with a reduced risk of myelosuppression, used either pre-emptively or prophylactically, maribavir being the most promising.

Another major complication of transplantation is acute GVHD, for which considerable progress has been made in prevention and treatment. Because the incidence of GVHD in allogeneic recipients is high even with treatment, as are the resulting morbidity and mortality, prevention of GVHD remains a high priority.

The optimal strategy for the prevention of GVHD is not yet clear. Two general approaches proven to reduce the incidence of acute GVHD are immunosuppressants, most commonly cyclosporine and methotrexate, and the removal of T-cells from the allograft. T-cell depletion is associated with adverse consequences, especially an increased risk of relapse [2]. Both cyclosporine and methotrexate have been proven in clinical trials to reduce the incidence of severe acute GVHD, with no clear superiority for either agent, but as many as 40% to 50% of patients who receive prophylaxis still develop significant GVHD. Combinations of both cyclosporine and methotrexate appear to reduce the risk of acute GVHD and improve survival rates when compared to either agent alone.

Clinical trial results during the 1990s make the combination of cyclosporine and methotrexate standard prophylaxis for GVHD in allogeneic recipients. Even with combination therapy, the incidence of GVHD is 25% to 30%. Additional clinical trials have explored the benefit of a 3-drug regimen that includes corticosteroids as well as cyclosporine and methotrexate, corticosteroids being the most effective drug for initial therapy of established GVHD. These trials have produced mixed results, suggesting no clear benefit from the addition of corticosteroids to cyclosporine/methotrexate for the prevention of GVHD and a possible increased risk of infection with more myelosuppression.

Newer immunosuppressants also offer opportunities for better GVHD prevention. Trials comparing tacrolimus and methotrexate with cyclosporine and methotrexate have demonstrated a decreased incidence of acute GVHD in both related and unrelated donor transplant recipients. Although the use of tacrolimus was actually associated with lower survival rates despite the decreased incidence of grade II-IV GVHD, this result may be attributable to the significantly higher percentage of patients with more advanced disease in the tacrolimus arm than in the control arm.

With these data, the combination of tacrolimus and methotrexate is becoming a more common prophylaxis regimen than cyclosporine and methotrexate. Despite these current prophylactic strategies, however, substantial numbers of patients still develop GVHD, and many have significant toxicities with current treatment approaches. The use of methotrexate is associated with both mucositis and liver toxicity.

The BMT-CTN has just opened a randomized clinical trial to investigate the effectiveness and toxicity, including mucositis and liver toxicity, of sirolimus combined with tacrolimus compared to methotrexate and tacrolimus in transplantation patients with HLA-identical sibling donors. The secondary endpoints for this trial include engraftment, chronic GVHD, thrombotic microangiography, and disease-free survival.

Table 2. Common and Potentially Devastating Viral Infections with No Known Prophylaxis

Adenovirus
Human herpes virus 6
Respiratory viruses
Polyoma BK virus
Human neurotropic JC virus
Epstein-Barr virus

Many clinical trials have focused on the prevention of GVHD through T-cell depletion, the removal of alloreactive T-cells from the infused graft product. Multiple strategies include different selectivity and different ways to manipulate the graft product. Many trials have demonstrated success at reducing GVHD, but with an increased risk of graft failure and relapse. The latter is particularly relevant for those diseases for which alloreactivity plays a role in disease control, chronic myelogenous leukemia (CML) being the hallmark disease.

The BMT-CTN is currently conducting a phase II study to determine whether T-cell depletion using CD34 selection reduces GVHD without increasing the risk of graft failure or relapse. The single-arm study will also explore immune reconstitution associated with CD34 selection and may further our understanding of late immune recovery.

Corticosteroids are the first line of therapy for patients with severe acute GVHD. In standard first-line therapy, methoprednisolone initiated at a dose of 2 mg/kg has been shown to be as effective as higher dose therapy. For patients who are unresponsive to treatment, the dose may be increased, but many of these patients still do not respond. Failure of first-line corticosteroid therapy indicates a bad prognosis.

Although many second-line alternatives are available to treat acute GVHD, none is an optimal choice for GVHD unresponsive to corticosteroid therapy or for use in combination with corticosteroids to achieve better early control. Another randomized clinical trial is underway to test 4 drugs that could be combined with corticosteroids as the initial therapy for newly diagnosed GVHD, mycophenolate, the tumor necrosis factor-inhibitor etanercept, denileukin difitox, and pentostatin. A novel study design will evaluate the most promising combination to bring forward in a prospective phase III randomized clinical trial comparing combination treatment to corticosteroids alone.

Organ toxicity is another major complication of transplantation and is frequently related to pretransplantation conditioning regimens. Throughout the posttransplantation period, 5% to 50% of allogeneic recipients develop some form of lung toxicity such as idiopathic pneumonia syndrome. Current standard therapy with corticosteroids is suboptimal, and mortality rates are high.

Etanercept may interfere with the pathogenesis of idiopathic pneumonia syndrome, which is believed to be largely inflammatory, and may improve the response rates when combined with corticosteroids. A clinical trial is investigating etanercept, with the primary endpoint being response to treatment. Another novel feature of this study is that serum in bronchoalveolar lavage fluid will be obtained from all patients and evaluated to investigate the biology of the idiopathic pneumonia syndrome.

Most randomized trials have focused on the early posttransplantation period and have not addressed care strategies for the large and growing number of long-term survivors who face clinically significant complications such as chronic GVHD, late infections, organ toxicity, and secondary malignancies, along with diminished quality of life and functional status. Long-term care recommendations still await good clinical trials. Early mortality unfortunately reduces the number of patients at risk for late complications and therefore the number of patients who are eligible for clinical trials. Another difficulty is that whereas patients are generally "captive" while undergoing treatment at a transplantation center, once they return home they are much less accessible for enrollment into clinical trials; some complications are harder to diagnose, and some patients may not return to the transplantation center. Thus patient accrual for meaningful clinical trials to look at late posttransplantation complications requires better communication between transplant physicians and physicians who care for posttransplantation patients in the community.

Some clinical trials of patients in the late posttransplantation period are underway. A planned clinical trial will compare sirolimus, rituximab, and pulse corticosteroids added to the standard therapy with corticosteroids in a calcineurin inhibitor for patients who have chronic GVHD. Other clinical trials include a multicenter prospective randomized trial to investigate the promising agent mycophenolate mofetil. Efforts are also focused on collecting clinical trial data to guide supportive care recommendations in the late posttransplantation period. Most trials focus on the early effects after transplantation, but many ongoing trials within the BMT-CTN are collecting data on quality of life for transplant recipients. These findings will be used to plan future clinical trials to further our understanding of the quality of life defects experienced by some transplantation patients. For some BMT-CTN studies, such as the voriconazole trial, long-term outcomes may follow through the observational database mechanisms of the Center for International Blood and Marrow Transplant Research, which can also provide data on the late effects of early trial interventions.

Many BMT-CTN trials involve collection of specimens that will be examined for biologic determinants related to late adverse effects. For some common complications of hematopoietic cell transplantation, such as delayed immune reconstitution, all patients could be eligible for clinical trials. For example, a trial to compare the most appropriate time to initiate reimmunization, currently recommended at 1 year by the United States Centers for Disease Control, may discover markers that would indicate whether or not patients have adequate immune recovery by 1 year and may benefit from delayed reimmunization.

Conclusions

Although clinical trials in the hematopoietic cell transplantation setting present many challenges, previous randomized clinical trials have provided a reasonable body of evidence that stands behind our current supportive care practices. The BMT-CTN, a new platform for randomized trials in transplantation patients, is conducting high-quality trials to inform the next generation of supportive care providers. Clinical trials to guide prevention strategies and treatment in the late posttransplantation period are still needed and will require broad support from both academic and community partners to accrue sufficient numbers of patients and thus achieve adequate power to inform meaningful conclusions for optimal patient care.

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Posttransplantation Patient Care: Tailored Prevention and Management Strategies

CME Assessment Test

1. **Which of the following is true regarding treatment planning for transplantation patients?**
   A. Because of donor shortages, the NMPD requests that donor searches not be conducted unless transplantation is the only treatment option.
   B. Transplantation treatment is not an option for patients with secondary MDS.
   C. The search for a suitable donor should begin at the time of diagnosis.
   D. None of the above.
2. **Which of the following is true regarding the care of unrelated donor transplant recipients?**
   A. Immune suppression regimens are the same as for related donor transplant recipients.
   B. Finding an allele-level matched unrelated donor takes much longer than finding an allele-level matched related donor.
   C. Early transplantation is an option for patients who do not have a sibling donor but have a molecularly matched unrelated donor.
   D. None of the above.
3. **Which if the following is true regarding umbilical cord blood transplantation (UCBT)?**
   A. Adequate cell dose is important for successful outcome.
   B. Graft failure is rare in UCBT.
   C. GVHD rates are much lower with UCBT than with transplants from other sources.
   D. None of the above.
4. **Which of the following is true regarding cancer screening in long-term transplantation survivors?**
   A. Breast cancer rates in long-term survivors 10 years posttransplantation are higher than those in the general population.
   B. In addition to screening for secondary cancers, patients should have the same screening tests recommended for the general population.
   C. Nonmelanoma skin cancers are the most common secondary cancer posttransplantation.
   D. All of the above.
5. **In long-term posttransplantation survivors, death is most commonly due to which of the following?**
   A. Disease relapse.
   B. Cardiovascular disease.
   C. Complications of chronic graft-versus-host disease.
   D. Secondary cancer.
6. **Which of the following concepts underlie optimal routine follow-up for posttransplantation patients?**
   A. Prevention of complications that can be avoided in at-risk patients.
   B. Appropriate screening and intervention.
   C. Patient education.
   D. All of the above.
7. **Which of the following characterize the relationship of the referring physician and the transplantation patient?**
   A. When the patient is undergoing the transplantation procedure, the referring physician no longer needs to provide information to concerned family members.
   B. Patient relapse and other bad outcomes can be devastating to the referring physician.
   C. Referring practices rely on transplantation patients for much of their income.
   D. All of the above.
8. **Which of the following is true regarding interaction between transplantation physicians and physicians who care for transplantation patients in the community?**
   A. The transplantation physician should keep the community physician aware of adverse events that occur during transplantation.
   B. Requests by transplantation physicians for follow-up data can create difficulties for referring practices.
   C. Long-term adverse outcomes of transplantation that are familiar to transplantation physicians may be perplexing to the referring practice.
   D. All of the above.
9. **Which of the following is true regarding clinical trials of hematopoietic transplantation patients?**
   A. Few trials have included patients in the late posttransplantation period.
   B. Patient homogeneity makes patient accrual an easy task.
   C. Many referring physicians are actively involved in patient recruitment.
   D. None of the above.
10. **Effective prophylaxis is available for which of these common and potentially devastating viral infections in posttransplantation patients?**
    A. Human herpes virus 6.
    B. Adenovirus.
    C. Epstein-Barr virus.
    D. None of the above.

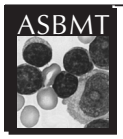
CME Assessment Test Answer Sheet

Release Date: March 31, 2007 **Last Review Date: March 31, 2007** **Expiration Date: March 31, 2008**

Instructions

(1) Read the articles in the publication carefully. (2) Circle the correct response to each question on the Answer Sheet. (3) Complete the evaluation Form. (4) To receive CME credit, fax the completed Answer Sheet and Evaluation Form to the office of Continuing and Professional Education (414-456-6623) or mail to the Office of Continuing Medical Education, Medical College of Wisconsin, 8701 Watertown Plank Road, Milwaukee, WI 53226. No processing fee is required.

1.	A	B	C	D	**5.**	A	B	C	D	**9.**	A	B	C	D
2.	A	B	C	D	**6.**	A	B	C	D	**10.**	A	B	C	D
3.	A	B	C	D	**7.**	A	B	C	D					
4.	A	B	C	D	**8.**	A	B	C	D					



CME Evaluation Form

Please evaluate the effectiveness of this CME activity on a scale of 1 to 5, with 5 being the highest, by circling your choice. Fax *with the Answer Sheet* to the Office of Continuing and Professional Education, 414-456-6623, or mail to the Office of Continuing Medical Education, Medical College of Wisconsin, 8701 Watertown Plank Road, Milwaukee, WI 53226.

Overall Quality of the CME Activity	1 2 3 4 5
Articles in the publication were presented in a clear and effective manner.	1 2 3 4 5
The material presented was current and clinically relevant.	1 2 3 4 5
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The CME activity provided a balanced, scientifically rigorous presentation of therapeutic options related to the topic, without commercial bias.	1 2 3 4 5

Please comment on the impact (if any) that this CME activity might have on your management of patients.

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I have read these articles on posttransplantation patient care, published in *Blood and Marrow Transplantation Reviews*, and have answered the CME test questions and completed the Evaluation Form for this activity.

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