Blood and Marrow TRANSPLANTATION

REVIEWS

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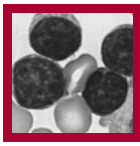

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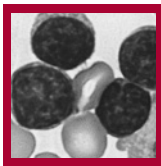
The Graying of Clinical Transplantation

John R. Wingard, MD, Editor

For decades transplantation clinicians have used age in decisions about candidacy for hematopoietic cell transplantation (HCT) It has often been joked that as transplanters have aged the "acceptable" age for HCT has increased. It has been assumed that age is a surrogate for likelihood for transplantation morbidity and mortality. Does the use of age in this way make any sense?

This issue contains a summary of a symposium that addressed the topic of age and HCT, held in Atlanta, Georgia, prior to the 2005 American Society of Hematology Annual Meeting. In the first presentation, Dr. William Ershler points out that the biological behavior and responsiveness to treatment of a number of cancers in the elderly appear to be no different than in younger patients, whereas for some cancers the behavior is different. Moreover, other factors (more frequent in the elderly) are probably more important than chronological age, including the presence or absence of comorbid diseases, frailty, functional status, and alterations in immune function that are yet incompletely understood. In the second presentation, Dr. Nelson Chao reviews the various transplantation strategies and how age and other factors influence which strategy is most appropriate for various considerations. In the third presentation, Dr. Edwin Alyea discusses the role of nonmyeloablative transplantation approaches in the older patient with comorbidities. In the final two presentations, Drs. Stephen Forman and Marcos de Lima discuss specific types of malignancies prevalent in the older patient and the role of nonmyeloablative transplantation.

Years ago, we recognized that patients at the early end of the age spectrum should not be treated like "small adults"; the biology of the diseases, tolerance to treatments, metabolism of drugs, and immune effects all are unique. It has only become accepted in recent years that individuals at the other end of the age spectrum similarly may have their own unique issues that require distinct tailoring of therapies. Age, per se, is too blunt a measure to capture the distinct care needs of this population. The advent of effective reduced-intensity conditioning regimens allows consideration of HCT for groups of patients once thought to be too fragile. Thoughtful examination of the heterogeneous biological and health issues in the elderly is now leading to a new and more thoughtful approach that will make our transplantation approaches more successful.



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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 Negrin Installed as President; Helen Heslop Elected Vice President

Robert Negrin, MD, professor of medicine and Director of the Division of Bone Marrow Transplantation at Stanford University, has been installed as president of the American Society for Blood and Marrow Transplantation.

Helen E. Heslop, MD, 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, is the newly elected and installed vice president, to become president in 2008.

The installation of officers and directors occurred at the BMT Tandem Meetings in February in Honolulu. The election was by mail ballot among members of the Society in January.

C. Fred LeMaistre, MD, of the Texas Transplant Institute, San Antonio, was re-elected treasurer.

Newly elected and installed directors are:

- H. Kent Holland, MD, of the Blood and Marrow Transplant Group of Georgia at Northside Hospital in Atlanta, Georgia.
- William Murphy, PhD, of the University of Nevada School of Medicine in Reno, Nevada.
- Neena Kapoor, MD, of Children's Hospital Los Angeles, California.

Robert Soiffer, MD, was elevated to president-elect and will assume the presidency in 2007. He is an associate professor of medicine at Harvard Medical School, chief of the Division of Hematologic Malignancies at Dana-Farber Cancer Institute, and co-director of Hematopoietic Stem Cell Transplantation at Dana-Farber and Brigham and Women's Hospital.

The new ASBMT president, Dr. Negrin, earned a bachelor of arts in biochemistry at the University of California-Berkley, and his medical degree cum laude in 1984 at Harvard Medical School. He was an intern, resident and fellow in hematology at Stanford University Medical Center. In 1990 he joined the faculty at Stanford University.

Dr. Negrin has been a member of the ASBMT Board of Directors since 2002 and has chaired its Committee to Study the ASBMT Mission. He is an associate editor for *Biology of Blood and Marrow Transplantation* and was Scientific Program Chair for the 2004 BMT Tandem Meetings in Orlando. He is a former president of the International Society for Cellular Therapy.

BMT Tandem Meetings Attendance Exceeds 2,000

The registration for the BMT Tandem Meetings in Honolulu was 2,030—a 25 percent increase over last year's record. Attendees came from 43 countries, including 139 from Japan, Australia, South Korea and 10 other Pacific Rim countries. A record 510 abstracts—a 50 percent increase over last year's record—were accepted from investigators in 35 countries.

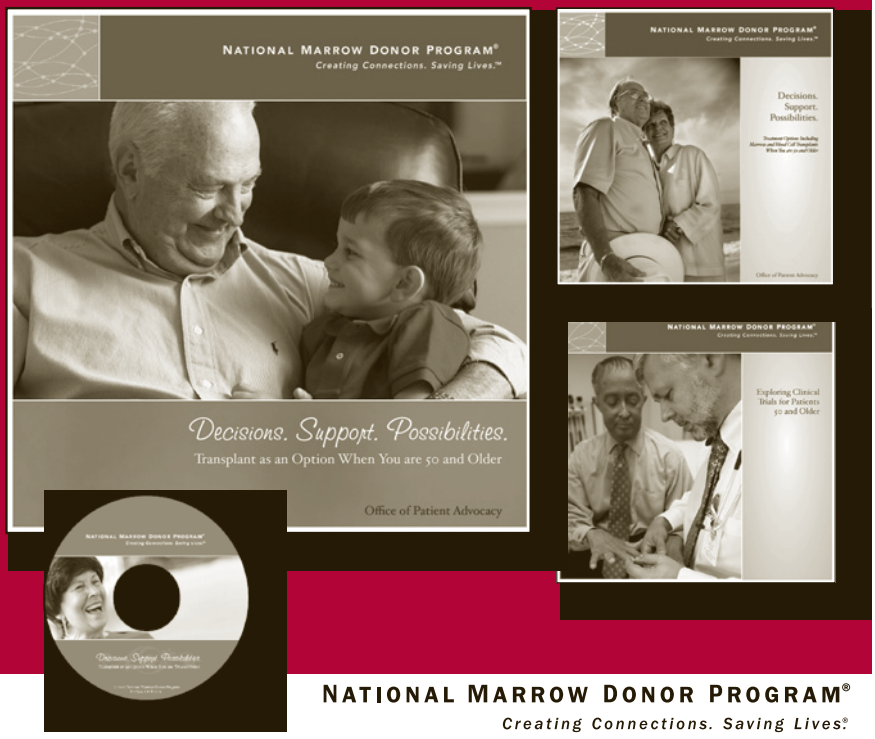
Meeting Abstracts Can Be Accessed Online

Abstracts accepted for the BMT Tandem Meetings were published in the February 2006 issue of *Biology of Blood and Marrow Transplantation* (Vol. 12, No. 2, Supplement). They also are indexed and accessible online at *www.abstracts2view.com/tandem*.

Lifetime Achievement Award Presented to Karl Blume

Karl Blume, MD, professor of medicine in the Division of Bone Marrow Transplantation at Stanford University Medical Center, is the recipient of the 2006 ASBMT Lifetime Achievement Award. He is one of the founders of ASBMT and in 1995 was a founding co-editor of *Biology of Blood and Marrow Transplantation*. The award, conferred during the President's Dinner at the BMT Tandem Meetings, is supported by a grant from Pfizer Inc.

New patient education materials for older adults considering transplant



Decisions. Support. Possibilities.

DVD, workbook and clinical trials brochure (for adults ages 50 and older)

Four patients over the age of 50 share stories about their decision to have a marrow or cord blood transplant and the medical, financial, and emotional concerns they had before making their decision.

The package of materials contains a DVD and two booklets that give patients in this age group tools they can use to talk to their family and their doctor about treatment choices.

To order a copy for your office or patients, visit **www.marrow.org/50plus**.

Subscribe to the National Marrow Donor Program's *Advances in Transplantation* e-newsletter for medical professionals and notices of upcoming NMDP education programs at **www.marrow.org/md**.

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ASBMT

Symposium Report

Blood and Marrow TRANSPLANTATION REVIEWS

Transplantation for the Older Patient: More Choices for Improving Outcomes

Adapted from a symposium held prior to the 2005 American Society of Hematology Annual Meeting on December 9, 2005, in Atlanta, Georgia. This symposium was jointly sponsored by the National Marrow Donor Program and the Medical College of Wisconsin.

MEDICAL COLLEGE OF WISCONSIN CME program

Faculty

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Stephen J. Forman, MD
City of Hope Comprehensive Cancer Center, Duarte, California

Nelson J. Chao, MD
Duke University, Durham, North Carolina

Marcos J. de Lima, MD
M.D. Anderson Cancer Center, Houston, Texas

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 presenting faculty have all made proper disclosure and the following relationships are relevant.

Dennis L. Confer, MD, has indicated he has nothing to disclose.

William B. Ershler, MD, receives honoraria as a speaker and a consultant for Amgen and as a consultant for Ortho Biotech, FibroGen, and Affymax.

Nelson J. Chao, MD, has indicated that he has nothing to disclose.

Edwin P. Alyea, MD, has indicated that he has nothing to disclose.

Stephen J. Forman, MD, has indicated that he has nothing to disclose.

Marcos J. de Lima, MD, receives honoraria as a speaker for PDL BioPharma and as a consultant for SuperGen.

Program Description

Transplantation is becoming widely accepted as an option for patients older than 50 years. These patients present different clinical scenarios than do younger patients, but with appropriate decision making in evaluation, treatment selection strategies, and supportive care, transplantation can be an effective option for older patients. This text focuses on the most recent outcomes data and provides practical considerations for evaluating and treating older patients who may benefit from transplantation.

Learning Objectives

After completion of this activity, participants will be able to:

- Identify factors to consider when evaluating an older patient for transplantation.
- Evaluate autologous versus allogeneic donor options for transplantation.
- Compare goals and outcomes of myeloablative versus reduced-intensity regimens.
- Describe patient selection criteria for transplantation for multiple myeloma, follicular lymphoma, and chronic lymphocytic leukemia in older patients.
- Describe patient selection criteria for transplantation for acute myelogenous leukemia and myelodysplastic syndromes in older patients.

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(s)™. 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

Transplantation is an attractive therapy because it offers a potential for cure, but frequently this option has not been available to older adults because the effects of transplantation toxicity are more pronounced in this population. Ten years ago, 50-year-old patients would have been considered too old for transplantation, but improvements in supportive care and innovations to decrease regimen-related morbidity and mortality are allowing more patients in this age group to undergo transplantation.

Because of new approaches that have been developed in the past several years, older patients are increasingly considered to be candidates for transplantation. At the National Marrow Donor Program (NMDP), we have seen tremendous growth in the use of donor or cord blood transplants for patients in all age groups, but particularly for those patients older than 50 years. In 1998, only 9% of NMDP transplantations were performed in patients older than 50 years; in 2004, 28% of NMDP transplantations were for patients older than 50 years. Now, more than 700 transplantations a year are performed for patients in this age group, who now make up the largest age group of NMDP transplantation patients.

These changes are occurring in all types of transplantation. Both allogeneic and autologous transplantations are increasingly used in older patients; 13% of allograft recipients and 53% of autograft recipients are older than 50 years, and 2% of allograft recipients and 20% of autograft recipients are older than 60 years. The NMDP has undertaken initiatives to address the older population and their transplantation needs, including developing educational materials and conducting survey research that addresses important issues from medical, social, and financial standpoints.

Most recently, the NMDP has developed a DVD and an accompanying workbook that contain information about risks and benefits along with financial and social considerations for patients older than 50 years who are considering transplantation as a treatment option. A clinical trials brochure specifically designed for patients older than 50 years is also available. This brochure discusses the value of clinical trials in improving transplantation outcomes. These materials are available through the NMDP Office of Patient Advocacy.

Special Considerations for Evaluation of Older Patients for Transplantation

William B. Ershler, MD

In assessing the eligibility of the older patient for transplantation, the primary caveat that must be kept in mind is that aging is not a disease. Disease does not necessarily accompany old age, and age alone does not obviate any therapy. With regard to transplantation, an older patient with no comorbidities is probably a candidate. Nevertheless, diseases, including most malignancies, increase in frequency with advancing age, and cancer is largely a disease of older people [1]. Although there are many reasons why this might be the case, perhaps most important is that it takes time to progress through the many steps of carcinogenesis and growth to reach a threshold for diagnosis. Other factors, including accumulated nonlethal damage to DNA (eg, by free radicals), increased proinflammatory factors, and age-associated declines in DNA repair and immune competence are to some degree important. The median age for all cancer is approximately 70 years and will become even older over the next several decades. Myelodysplasia and hematologic malignancies, including lymphoma, myeloma, and leukemia, can be effectively treated in older age groups, but advanced age presents a number of additional challenges. With appropriate pretreatment assessment of organ reserve, physical performance, and cognitive function, individualized (tailored) therapy may ultimately prove to offer the greatest chance for successful outcomes. Such assessment would also identify those who are likely to benefit from more aggressive treatments, including bone marrow or stem cell transplantation.

Old Age and Frailty

The population is aging. Currently, approximately 13% of the United States population is at least 65 years old, and by 2050 it will be about 20%. The fastest growing population group is the "old old," persons older than 85 years, which has reached fairly exponential growth over the past few decades. Of all the people over the age of 65, most are living in the community and rate their health as excellent or good, but the remainder need assistance with one or more activities of daily living (ADLs).

The phenotype of frailty, exhibited by a subset of individuals who do not necessarily have disease but become frail with age, is an area of intense interest in geriatric medicine. In the elderly population there is tremendous heterogeneity in health. Currently, frailty is considered to be a state of high vulnerability for adverse health outcomes, including disability, dependency, falls, need for long-term care, and mortality. Researchers such as Fried et al [2] are formulating scoring systems to better define this state and thereby facilitate the development of improved strategies for diagnosis and care.

Cytokine Imbalance with Aging

Certain cytokines are demonstrably reduced with age, including interleukin (IL)-2 and IL-12, whereas others (including IL-6 and IL-10) increase. The proinflammatory IL-6 is particularly interesting because its level may increase without clinically apparent inflammatory disease. Tumor necrosis factor α and IL-1 have been reported to increase with age, but these cytokines are almost always associated with underlying inflammatory disease. In contrast, IL-6 and IL-10 may increase without evident inflammatory disease. IL-6 is a very powerful molecule that is physiologically relevant during an inflammatory reaction. It stimulates catabolic processes, inducing inflammatory responses such as mobilizing calcium from bone. IL-6 also might be involved in the dysutilization of iron with inflammatory disease, so some of the anemia seen with advancing age can be explained through this mechanism. Under quiescent circumstances, IL6 is present at levels that challenge detection with even the most sensitive assays in younger adults, but because of age-related increases associated with menopause and andropause it becomes detectable in older adults, and this detection may be related to the presence of inflammatory disease or to normal aging, frailty, or age-associated anemia.

It is possible to define a mechanism for anemia that occurs in late life only in approxi-

mately one fourth of the cases. Anemia in the elderly is associated with inflammatory cytokines, and individuals found to have a high level of these mediators (IL-6 and others) are most likely to have lower erythropoietin and a diminished marrow response to anemia. Mortality rates are higher in individuals in whom both C-reactive protein and IL-6 are increased. High IL-6 is associated with less mobility, more depression, and more dementia.

Cancer and Age

The main reason older people get more cancer could be that it takes a long time to develop epithelial cancers such as colon and lung cancer. The model for colon cancer, for example, postulates 7 to 10 steps that occur in stochastic fashion before cancer is recognizable, and this process may take decades. This model certainly explains why colon cancer is rare in children. Another factor is mutation frequency, which increases with age and, coupled with faulty or declining DNA repair and free radical damage, leads to increased cancer incidence.

Although older people are more likely to have cancer, cancer may be less malignant in older people. Geriatric patients with metastatic breast cancer may survive a decade or more, a situation that is unheard of in young patients. In animals with tumors, paradoxically, immune senescence seems to be beneficial. In humans, elderly patients generally present with more advanced disease for a number of reasons. There is a bias against using aggressive treatments in older patients, but this bias usually comes from physicians, nurses, and family and less frequently from the patients themselves, who almost invariably select the treatment that gives them the best chance of living. Treatment outcomes are, in general, comparable in younger versus older patients receiving nonemergency surgery, elective radiation, and even chemotherapy. The data reveal that the response rates are generally the same. The problem is that very few old people are included in clinical trials, and the old people in clinical trials are not representative of the "typical" community older patient. Instead, large trials typically include elderly who have excellent performance and limited comorbidity [3]. There is a need for more elderly individuals with conditions such as frailty and comorbidity to be included in clinical trials.

Comorbidity and Transplantation: Treatment Decision Making

Older patients often require tailored treatments, particularly because of the likelihood of comorbidities. The number of comorbidities increases dramatically with age, and these comorbidities are very important in making decisions about transplantation. For example, the likelihood of a 45-year-old woman with breast cancer dying from this condition is substantial; but a woman over the age of 75 who has other comorbidities with the newly diagnosed breast cancer remains more likely to die from one of the comorbidities. So in older patients a functional assessment is essential. Traditionally, oncologists use a rudimentary performance measure such as the Eastern Cooperative Oncology Group scale (ECOG) [3], and such scales prove to be very adequate for young patients. But in older people, the performance scale that is used for younger patients is not sufficient. We need a better way to assess which patients can or cannot undergo the rigors of transplantation.

Functional Assessment

A simple performance-based assessment of ADLs can be done in 1 to 5 minutes and may offer additional predictive value. For example, in our studies in anemia and anemia correction, we use "get up and go" as a predictor of survival. A comparison of ADLs in individuals older than 70 years indicates that their 2-year mortality rate if they are fully independent is 8%, but dependence in ADLs increases their 2-year mortality rate to nearly 25%.

Conclusion

Most cancers, including leukemia and lymphoma, occur more frequently in patients at an advanced age. By improving supportive care, reducing intensity of the conditioning regimens, and providing more tolerable graft-versus-host disease prophylaxis, we have extended transplantation and other treatment options to older persons. With patients older than 50 years there is a need for geriatric assessment that is a little bit more than an ECOG performance scale and that addresses comorbidity, but to date there are not a lot of data to support this extra pretreatment analysis. We need to identify the individuals who are at risk and tailor our transplantation strategies accordingly, particularly for the rapidly expanding group of individuals older than 70 years. In general, conditions such as breast cancer and lymphomas in otherwise healthy individuals are likely to be as effectively treated as those in younger patients, with notable exceptions that include acute myelogenous leukemia and Hodgkin disease, both of which may actually be different diseases when diagnosed in late life. Older people are more likely to have comorbidities, organ impairment, and functional impairment that might preclude full-dose cancer therapy. With effective tools for pretreatment functional assessment and comorbidity, we might be able to develop transplantation strategies for patients for whom such treatment might otherwise have been precluded on the basis of age alone.

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Transplantation Options: Autologous versus Allogeneic

Nelson J. Chao, MD

A growing understanding of biological rationales has enabled stem cell transplantation to evolve from a treatment of last resort to frontline therapy for selected diseases. New therapies involve autologous and allogeneic cell sources, chemotherapy, and combination treatments, and ongoing research continues to reveal more effective therapies.

Overview

After the atomic bomb explosions at the end of World War II, there was a great deal of interest in the effects of radiation injury. It became clear that bone marrow was exquisitely sensitive to radiation and that "low" levels of exposure could lead to bone marrow failure and death.

Early murine studies provided important information:

- Intravenous bone marrow administration was as effective as any other route.

• Donor marrow cells could mount an immune attack, causing a "secondary disease," graft-versus-host disease (GVHD).
• The severity of GVHD was determined by genetic factors.
• Histocompatibility was governed by 1 major and many minor determinants.
• Different subtypes of immune cells were important in these processes.

After animal studies had been performed in mice and dogs, bone marrow transplantation was attempted in humans. The first reported cases were largely unsuccessful, but by 1959, 3 reports suggested the potential of this treatment approach. One case was a young girl with acute lymphoblastic leukemia who received a marrow transplant from a syngeneic twin after total body radiation and recovered rapidly. In 2 other cases, there was very rapid recovery following autologous transplantation.

Initially, transplantation treatment focused primarily on the fact that the bone marrow contains hematopoietic stem cells and is an organ that can be transplanted from donor to patient. The number of allogeneic transplantations plateaued, but rose again in the past few years with the increased use of nonmyeloablative transplantation. The number of allogeneic transplantations increased since the report of favorable outcomes data from the Center for International Blood and Marrow Transplant Research [1] (Figure 1). Much research focused on treatment with autologous and allogeneic transplantation compared to chemotherapy for the treatment of hematologic malignancies [2-4].

Recently in North America, the indications for transplantation have been allogeneic primarily for the leukemias and autologous primarily for myeloma, lymphoma, and Hodgkin's disease (Figure 2).

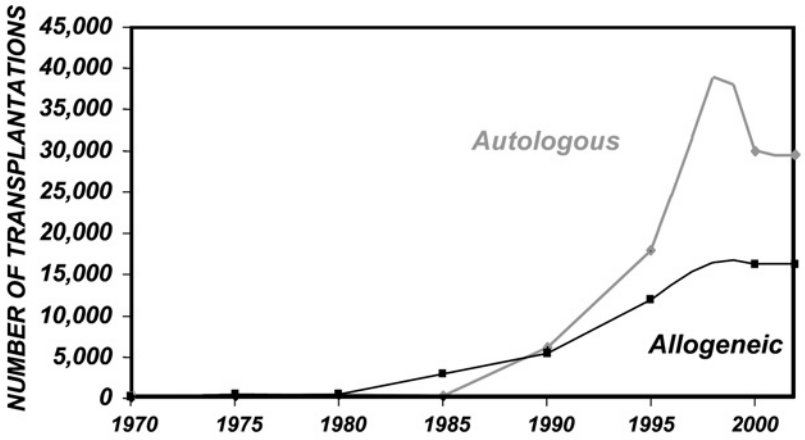

Figure 1. Annual numbers of blood and marrow transplantations worldwide, 1970-2002.

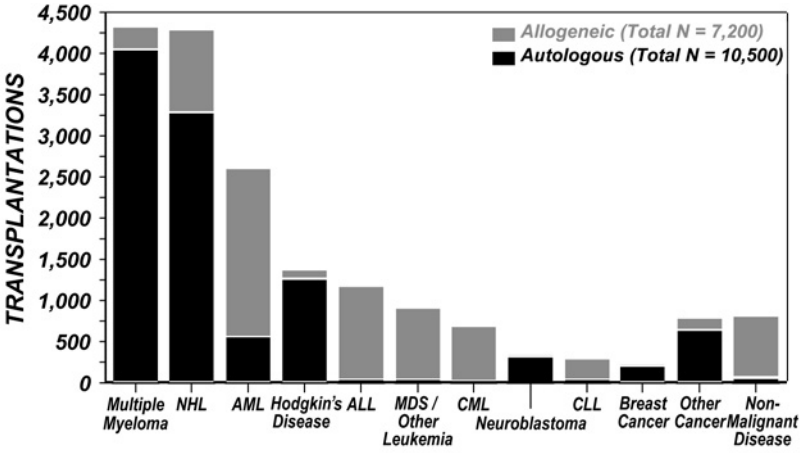

Figure 2. Indications for blood and marrow transplantation in North America.

Treatment Rationales and Outcomes

The original goals of allogeneic transplantation were to treat the underlying disease with higher doses of radiation and chemotherapy, to create "space" or niches for engraftment in the bone marrow, and to immunosuppress the recipient to prevent rejection due to the host-versus-graft effect. It later became clear that bone marrow transplantation involved not only treating the underlying disease by reconstituting an organ, as in transplanting a heart, but also bringing in a new immune system.

In contrast, autologous transplantation is fairly simple. When this treatment was first used there was no known immunological effect, and although we now think there may be an effect, the goal of autologous transplantation, dose intensification, has not changed over time. Dose intensification can improve the chances of cure with certain drugs that have a steep dose response curve. Dose intensification is not appropriate in all cases, however. Many tumors, such as stage 2A Hodgkin's disease, can now be cured with standard doses of chemotherapy, so dose intensification is unnecessary. There are other tumors, such as metastatic colon cancer and lung cancer, for which drug resistance cannot be overcome by giving higher doses. The use of dose intensification is appropriate for those patients in whom bone marrow toxicity, which can be addressed in the autologous transplantation setting, is the only limiting factor for administering curative drug doses that destroy all malignant cells.

Allogeneic transplantation offers the advantages of high doses of chemotherapy or radiation along with a net effect from the graft as well, the graft-versus-leukemia or graft-versus-tumor factor. This effect, however, carries with it the increased mortality risk from acute or chronic GVHD. Other complications include delayed immune recovery, which can be quite significant, and organ toxicity from the treatment. Some organ toxicity is also possible with autologous transplantation, but the major concern is disease recurrence.

Outcome Comparisons

Regarding causes of death in transplantation, in the autologous setting the major problem is relapse; most patients do suffer relapse, whereas organ toxicity is less of a problem. In identical sibling transplantation, the relapse

rate is approximately half of that in the autologous setting, but other problems occur, such as infection, organ toxicity, and GVHD. Similar problems occur with unrelated transplantation, but with lower relapse rates, because there seems to be more of a graft-versus-tumor effect, but higher rates of GVHD. In addition, more intensive immune suppression for treatment of GVHD leads to higher infection rates.

When these factors are weighed, it is apparent that in general patients of a younger age would most benefit from allogeneic transplantation. Patients who have been heavily pretreated, have significant comorbidities, or have poor performance status may benefit most from autologous transplantation. Patients who do not have an HLA-matched donor should consider autologous transplantation over allogeneic transplantation. With advanced disease stage, however, allogeneic transplantation is probably the best treatment because of the benefits of the preparatory regimen and a new immune system and because relapse is a major problem with autologous transplantation. In some cases, the choice of allogeneic or autologous transplantation depends on the disease being treated, because certain diseases might be better controlled with an immune-mediated response.

Nonablative transplantation is, in essence, adopted immunotherapy through broad grafting of donor cells to provide a new immune system that will recognize the allogeneic tumor cells. High-dose chemotherapy is avoided, and the treatment focus is on the antitumor effect from the graft. The recipient receives low doses of radiation or standard doses of chemotherapy to remove the host response against the graft, which then allows the achievement of a state of mixed chimerism. With the administration of donor leukocyte infusion, complete donor chimerism is induced in the recipient, and when this is successful the anti-tumor effect can be quite potent.

Looking Ahead

Just as the first researchers in bone marrow transplantation were on the threshold of discovering the many treatments and procedures available today, we are on the threshold of the development of even more beneficial methods to treat patients of all ages. Current research is directed toward better disease stratification, facilitated by prodiomics and genomics, to understand which patients could benefit from which treatments. We are developing better antitumor drugs and working on augmentation of the preparatory regimen with monoclonal antibodies or radioimmunoconjugates. Other research is exploring posttransplantation graft engineering with antibodies or adopted T-cell immunotherapy, enhanced mobilization for stem cells engraftment in autologous transplantation, and prevention of GVHD without the loss of the graft-versus-lymphoma effect in allogeneic transplantation.

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Making the Decision: Myeloablative versus Reduced-Intensity Regimens

Edwin P. Alyea, III, MD

Advanced age is often identified as an adverse prognostic factor for patients undergoing myeloablative allogeneic transplantation. Although selected older patients may be treated successfully with myeloablative allogeneic transplantation [1], high rates of treatment-related mortality prevent many older patients from receiving this treatment. Over the past few years, nonmyeloablative or reduced-intensity conditioning regimens have been offered as alternatives to myeloablative high-dose chemo/radiotherapy for older patients undergoing allogeneic hematopoietic stem cell transplantation [2-6]. These less intense preparative regimens are less toxic and better tolerated by older patients, and their use results in decreased early treatment-related mortality compared with myeloablative transplantation. Unfortunately, long-term complications, such as chronic graft-versus-host disease (GVHD), remain significant complications of the procedure, and older patients may have greater difficulty tolerating these adverse effects.

Myeloablative Transplantation in Older Patients

The reasons for increased treatment-related mortality in older individuals include the presence of comorbid conditions such as renal, cardiac, or pulmonary abnormalities. Older patients often suffer complications from the treatments used prior to transplantation and may also be more likely to suffer GVHD after transplantation, particularly in match-related settings with elderly donors. With improvement in supportive care and other aspects of myeloablative transplantation through the years, however, outcomes have improved even for older individuals.

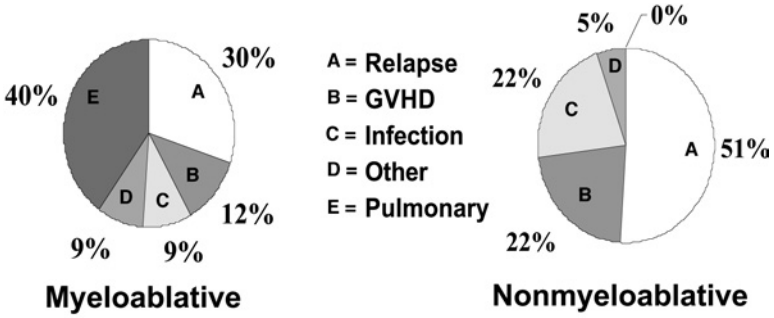
Studies in which most patients were older than 50 years demonstrated that myeloablative transplantation can be performed in selected elderly patients. Wallen and colleagues [1], in a study of myeloablative transplantation for patients older than 60 years, demonstrated overall and relapse-free survival rates of approximately 34% in those patients with long-term follow-up. The treatment-related mortality was elevated in 43% of these elderly patients, and relapse, which remains a challenge in any transplantation setting, accounted for 24% of the treatment failure in this group.

Nonmyeloablative Transplantation as a Treatment Alternative

Nonmyeloablative transplantation is used with increasing frequency as an alternative to myeloablative transplantation in older adults to improve outcomes and reduce nonrelapse mortality. Despite this shift in treatment practices, there are limited data available comparing the outcomes after nonmyeloablative versus myeloablative allogeneic transplantation. Representative studies have addressed the outcomes for older individuals undergoing nonmyeloablative transplantation for patients older

than 55 years who received either matched related or unrelated donor transplants. Overall survival rates ranged from 44% to >68%, and treatment-related mortality largely reflected the population of patients treated in the studies.

Nonmyeloablative transplantation offers several potential advantages over myeloablative transplantation. Treatment-related toxicity is reduced, making the regimen more tolerable for patients with comorbid disease. In addition, nonmyeloablative transplantation may be associated with less acute GVHD. Finally, nonmyeloablative transplantation may offer the opportunity for lower cost and improved quality of survival.



Causes of treatment failure in myeloablative and nonmyeloablative transplantation.

Choosing between Myeloablative and Nonmyeloablative Transplantation

An individualized approach should be taken when choosing between these two treatment options for older individuals. Nonmyeloablative transplantation should be considered for patients with a high comorbidity index [7] or prior myeloblative transplantation. The potency of the graft-versus-malignancy (GVM) effect and the role of dose intensity in the cure of the disease are also important considerations when choosing between these approaches.

Nonmyeloablative regimens are advantageous in cases in which disease is susceptible to a GVM effect, but avoidance of high-dose chemotherapy and radiation may increase the risk of relapse in patients with diseases for which high-dose therapy is important in achieving a cure. Thus the success of nonmyeloablative transplantation depends on its ability to decrease treatment-related mortality sufficiently to compensate for the degree of antitumor activity lost as a consequence of less intensive chemotherapy or radiotherapy.

At the Dana-Farber Cancer Institute, a comparison of patients older than 50 years who received either nonmyeloablative or myeloablative transplantation demonstrated an equivalent overall and progression-free survival despite the high-risk features of the patients receiving nonmyeloablative transplants [8]. Treatment-related mortality was increased after myeloablative transplantation, and risk of relapse was increased after nonmyeloblative transplantation.

The nonmyeloablative treatment strategy that we have used at Dana-Farber includes a conditioning regimen in which patients receive fludarabine 30 mg/m^2 per day for 4 days and on the same days a single infusion of IV busulfan at 0.8 mg/kg per day. All patients receive either a tacrolimus- or cyclosporine-based GVHD prophylaxis regimen.

We compared 71 patients receiving a nonmyeloablative transplant with 81 patients receiving a myeloablative transplant. The patients in the nonmyeloablative group had a median age of 58 years compared to 54 years in the myeloablative group. In both groups the majority of patients had acute myelogenous leukemia, but in the nonmyeloablative group there were more patients with myelodysplastic syndrome and in the myeloablative group more patients with chronic myelogenous leukemia. More patients undergoing nonmyeloablative transplantation received unrelated donor transplants, and 93% of nonmyeloablative patients received peripheral blood stem cells compared to only 28% of myeloablative patients.

The majority of patients undergoing myeloablative transplantation had received cyclophosphamide and total body irradiation. Prior myeloablative transplantation had been performed in 25% of the nonmyeloablative patients and only 4% of the myeloablative patients. It is important to note that 85% of the patients in the nonmyeloablative group had active disease compared to 59% in the myeloablative group. The primary indications for the patients undergoing nonmyeloablative transplantation were advanced age in 56% of the patients, prior myeloablative transplantation in 24%, and disease type in 13% (ie, patients with chronic lymphocytic leukemia or multiple myeloma or the presence of comorbid illness). Despite the high-risk features of the nonmyeloablative group, the nonmyeloablative and myeloablative outcomes were similar for overall survival and progression-free survival rates, and the incidence of GVHD did not differ between these two patient populations.

Again, there is a trade-off in this population between relapse and treatment-related mortality. Nonmyeloablative transplantation was associated with a higher relapse rate than myeloablative transplantation, whereas treatment-related mortality, as expected, was lower in the nonmyeloablative group than in the myeloablative group. For the majority of nonmyeloablative patients who suffered treatment failure, relapse was the principal cause, with infection and GVHD being the other major reasons (Figure). For myeloablative patients, however, treatment-related factors such as infection, GVHD, and pulmonary complications were more important causes of treatment failure than relapse.

We constructed models to predict the outcomes for patients older than 50 years to discern which factors may be important in choosing between these two modalities (Table). In this multivariate analysis, conditioning regimen did not have an impact on progression-free survival. Donor source (related versus unrelated donor) and the development of acute GVHD also showed no impact on progression-free survival. The two factors that did appear to predict or influence progression-free survival were patient/donor sex mismatch and remission status, with patients undergoing transplantation in remission having better outcomes than patients with active disease.

Models to Predict Outcome for Patients Older than 50 Years

Variable	Progression-Free Survival (Hazard Ratio)	*P*
Conditioning regimen	0.7	NS
Donor sex mismatch (mismatch versus same)	0.6	.03
Donor type	1.0	NS
Acute graft-versus-host disease	0.9	NS
Stem cell source	0.9	NS
Remission status	0.6	.03

In conclusion, despite the adverse prognostic features of patients receiving a nonmyeloablative transplant, patients older than 50 years had similar overall and progression-free survival rates after nonmyeloablative or myeloablative transplantation. As expected, early treatment-related mortality was reduced after nonmyeloablative transplantation, but relapse of disease was more likely.

So how should these different factors be evaluated when treating an individual who must choose between myeloablative and nonmyeloablative strategies? Factors that should be considered include the presence of comorbid disease or a history of previous transplantation, both of which suggest nonmyeloablative transplantation as an option. The graft-versus-leukemia (GVL) effect in specific diseases also must be considered. Nonmyeloablative transplantation should be pursued in cases in which the GVL reaction is strong and can mediate potential cure. Dose intensity also plays a role in the potential cure of specific diseases. In some situations or disease states, dose intensity does not play a role in cure, and therefore the better option may be for nonmyeloablative rather than myeloablative transplantations. In some situations, the converse may be true.

The issues of cost and quality of life must also be considered. It has been well documented that solid-organ toxicities are higher in those patients undergoing myeloablative transplantation. The development of specific comorbidity indices will help in decisions related to quality-of-life issues. In terms of cost comparison, nonmyeloablative transplantation is associated with lower costs across the board. Therefore, if we are able to improve nonmyeloablative transplantation by reducing the incidence of relapse, its lower cost and improved quality of life will make it a valuable treatment option.

Summary

Nonmyeloablative preparative regimens allow older individuals with comorbid disease to undergo allogeneic transplantation. Patients who undergo nonmyeloablative transplantation have lower rates of early treatment-related mortality than patients undergoing myeloablative transplantation, but nonmyeloablative patients are at risk for late complications such as chronic GVHD. Despite these risks, our study of patients older than 50 years showed that nonmyeloablative patients had rates of overall and progression-free survival similar to those of myeloablative patients. Relapse rates, however, were higher after the nonmyeloablative approach. For some disease conditions, the value of nonmyeloablative transplantation in older patients may be largely related to the GVL effect and not regimen intensity. Future study should focus on methods to reduce the risk of relapse after allogeneic transplantation.

The choice between nonmyeloablative and myeloablative transplantation should be individualized and not made simply on the basis of age. The presence of comorbid disease or a history of prior transplantation treatment should influence the decision, as well as the role of dose and the impact of the GVM effect in specific diseases. Future trials will clarify the role of nonmyeloablative transplantation in these areas.

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Transplantation for Low-Grade B-Cell Malignancy: Low-Grade Lymphoma, Multiple Myeloma, and Chronic Lymphocytic Leukemia

Stephen J. Forman, MD

Hematopoietic stem cell transplantation is an effective therapy for selected patients with low-grade B-cell malignancies such as multiple myeloma, low-grade lymphoma, and chronic lymphocytic leukemia (CLL). Although these disorders are more common in older patients, studies of full allogeneic transplantation for the treatment of these disorders have been performed primarily in younger patients. Patients who are undergoing transplantation treatment for these illnesses are primarily in their late 30s and 40s, but the average age of diagnosis is almost 2 decades older. Although studies of full allogeneic transplantation have been encouraging in low-grade lymphoma and CLL and in some patients with myeloma, most of the patients who actually suffer from this disorder are excluded from this treatment approach because of transplantation-related toxicity.

In addition to being more common in older patients, these disorders share a strong sensitivity to the graft-versus-tumor (GVT) effect associated with allogeneic transplantation. On the basis of these observations, studies are being conducted to explore the efficacy of reduced-intensity allogeneic transplantation treatment for each of these disorders.

The GVT Effect in Allogeneic Transplantation for Hematologic Malignancies

Preliminary results suggest that the GVT effect could be a useful clinical strategy for inducing remissions in patients with low-grade B-cell disorders. The evidence for a GVT effect in allogeneic transplantation includes the observations that (1) relapse rates are higher in patients who receive transplants from an identical twin than in patients who receive transplants from HLA-matched siblings, (2) a graft-versus-host reaction is correlated with a reduced chance of relapse, (3) in

patients who do relapse, disease regression sometimes occurs with the withdrawal of immunosuppression, (4) donor lymphocyte infusions are sometimes effective for treating relapse, and (5) reduced-intensity transplantation is effective in inducing durable remissions in some diseases of hematopoietic origin.

Disease sensitivity to the GVT effect is not the same for all the hematologic malignancies. Although most of these malignancies can be cured by an allogeneic transplantation, the contribution of the graft to cure varies by disease. Chronic myeloid leukemia (CML), low-grade lymphoma, myeloma, and CLL are disorders that appear to be very sensitive to this effect. Acute lymphocytic leukemia (ALL) is less sensitive, although there is some graft-versus-ALL effect.

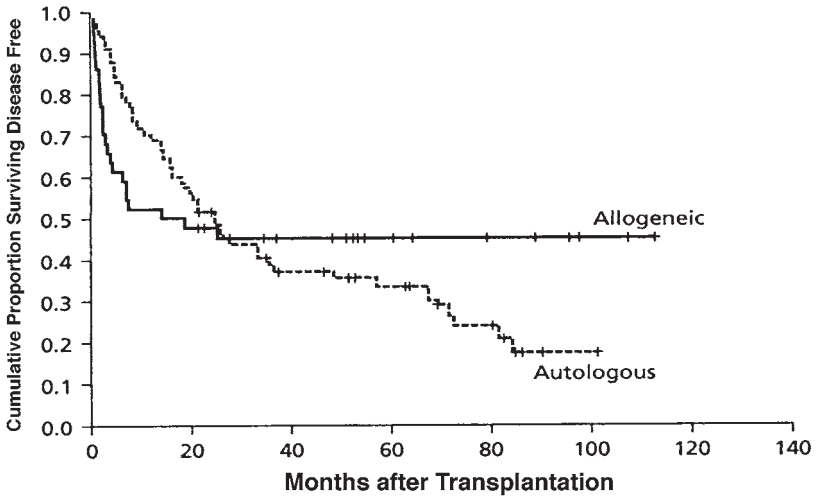

Figure 1. Survival curve after autologous transplantation for low-grade lymphoma shows that long-term survival is possible but disease-free survival is unlikely.

Transplantation for Low-Grade Lymphoma, CLL, and Multiple Myeloma

In cases of low-grade lymphoma, CLL, and multiple myeloma, a better understanding of the nature of the tumor cell and its heterogeneity enables physicians to make more informed decisions about the timing and type of treatment. Increased numbers of effective therapies for low-grade lymphoma are extending the time from diagnosis to when transplantation should be considered. Other aspects that affect this decision are prognostic signs that reflect clinical biology, response to therapy and its duration, cytogenetics, and molecular profiling.

Because low-grade lymphoma is a disease of older people who are likely to have siblings who cannot provide stem cells because they are also older and have comorbidities, unrelated donor transplantation may be an important option. Stem cell collection for autologous transplantation may also be a problem, particularly in patients who have been treated with melphalan, radioimmunoisotopes, or multiple prior regimens. In addition, the more therapy a person has had, the more likely it is that stem cells collected for transplantation have sustained genetic damage that will, in some patients, lead to myelodysplasia in the posttransplantation setting. Transplantation for low-grade lymphoma has most commonly been performed in patients in second or third remission, but the therapeutic contribution of antibodies and radioimmunoconjugates to disease management enables patients in this group to undergo transplantation later in the course of their disease.

The probability of survival after autologous transplantation for low-grade lymphoma is shown in Figure 1. Patients may live for a long time, but there is not a high probability of disease-free survival after autologous transplantation because recurrences are very common. The lack of a plateau in the survival curve indicates that the disease is not often cured by the autologous approach using standard transplantation regimens.

In trials of allogeneic transplantation for low-grade lymphoma, there appears to be a strong allogeneic response with long-term disease control in surviving patients, and the problems of poor collection of cells, cytogenetic abnormalities, and myelodysplasia are avoided.

A nonmyeloablative approach has been used in low-grade lymphomas to combine tumor sensitivity to the allogeneic T-cells with a less toxic regimen to make this treatment available to older patients who are not candidates for autologous transplantation because of the poor prognostic features of their disease or the extent of prior treatment. The studies to date suggest that remissions achieved with this approach appear to be as durable as those obtained with fully ablative regimens for low-grade lymphoma.

Full allogeneic transplantation treatment for myeloma is associated with greater toxicity than transplantation for patients with AML, ALL, or CML who are the same age and have similar apparent comorbidity factors. For the most part, full ablative allogeneic transplantation for myeloma has not been a commonly used treatment, even in younger patients. Therefore, high-dose therapy followed by either autologous or allogeneic stem cell transplantation (or both) is being explored as a promising means to increase remission rates and improve survival [1].

Early studies indicate that many patients with myeloma can achieve a full morphologic and molecular remission after sequential autologous and allogeneic transplantation. These studies, which are ongoing, will help determine the relative efficacy of each approach in the management of the disease. Because high transplantation-related mortality is the major limitation to the use of allogeneic transplantation in multiple myeloma, the use of nonablative conditioning regimens may make this treatment available to more patients [2].

Most indications for transplantation for CLL are based on the phenotypic and genetic evaluation of the leukemia cells and response to initial treatment and its duration. Patients who have a complete response with a short time to progression, poor or short response to initial therapy, or transformed disease may be candidates for transplantation.

In CLL, in contrast to other types of lymphoproliferative disease, chemosensitivity may not be a necessary selection criterion for patients undergoing allogeneic transplantation for CLL because disease-free survival appears to be similar in chemosensitive and chemorefractory patients. Because of the strong allogeneic immune effects in CLL, allogeneic

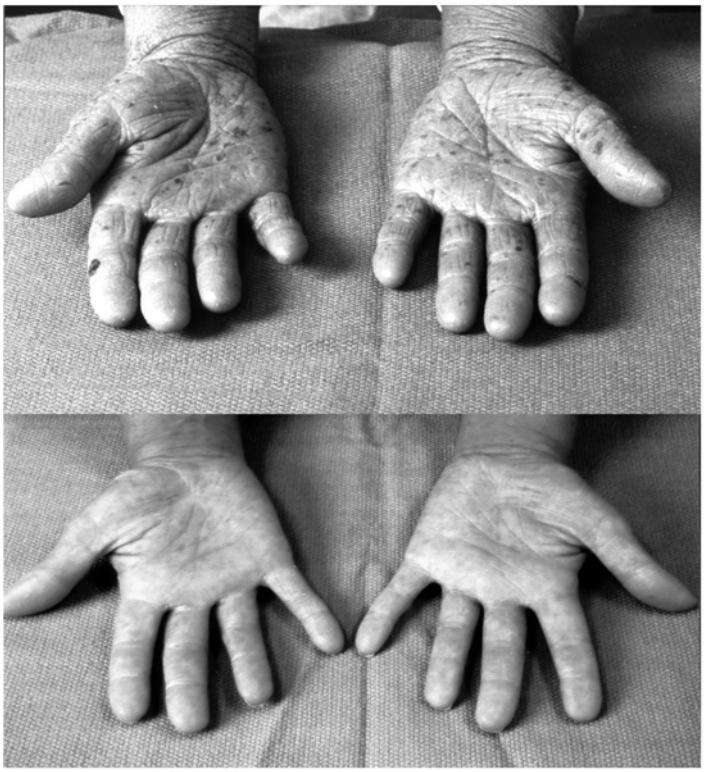

Figure 2. Mycosis fungoides erythroderma before and after reduced-intensity allogeneic transplantation.

transplantation may overcome chemotherapy refractoriness in CLL patients and should be considered as a treatment option even in fludarabine-refractory cases [3,4].

Mycosis fungoides (MF), a cutaneous T-cell lymphoma, is a low-grade lymphoma with long survival but with poor quality of life and disfigurement. This disease has a variety of manifestations in the skin, from patch to tumors to diffuse erythroderma. Lymph node involvement occurs at an advanced stage, along with the presence of progressive skin involvement and Sezary cells in the blood. Patients with Sezary syndrome often have extensive symptomatic generalized dermatitis.

Stem cell transplantation for MF has sometimes been used to treat patients in the advanced stage. Studies of autologous transplantation in MF have shown a good clinical response, with skin clearing, but in the vast majority of patients the disease recurs within 3 to 6 months. Given the strength of the graft-versus-lymphoma effect, studies have been conducted on the use of allogeneic transplantation to harness the same GVT effect in this disease. In one study of allogeneic transplant recipients, 8 patients who had MF with extensive skin involvement all achieved remission, and 6 of the 8 became long-term disease-free survivors [5]. Three of these patients who had a poor performance status because of disease were treated with a reduced-intensity approach with a good clinical result (Figure 2).

Ongoing Studies

Currently, a national trial sponsored by the NIH (NHLBI/NCI) Blood and Marrow Transplant Clinical Trials Network (BMT CTN) is ongoing in multiple myeloma to determine the relative efficacy of autologous followed by reduced-intensity allogeneic transplantation compared to a tandem autologous transplantation. This study will help determine the relative efficacy of each approach in inducing complete remissions and the durability of the remissions in patients with good- or poor-risk disease based on their risk factors at the time of diagnosis and the time of transplantation.

National studies are also being planned to determine the efficacy of reduced-intensity allogeneic transplantation in patients with relapsed low-grade B-cell lymphoma. Although there are fewer studies in CLL, phase II studies conducted at several institutions indicate that the GVT effect can induce remission and overcome fludarabine resistance and should be a therapeutic consideration for patients who fail or do not respond adequately to fludarabine-based therapy. Thus, progress in understanding the nature of engraftment and the GVT effect is increasing the therapeutic possibilities for patients with these diseases, even in an older population. In these clinical trials, the cell biology correlates that accompany the analysis will provide a basis for the next stage of treatment progress.

Conclusions

Based on progress in our understanding of how an allogeneic transplantation mediates a cure and the development of safer transplantation regimens that harness this therapeutic effect, older patients need not be denied the potential benefits of transplantation in management of their disease. Over the last 5 years, our transplantation survivors are getting older not just because they are living longer but also because older patients are coming into the transplantation program for the same treatment, with hopefully similar outcomes.

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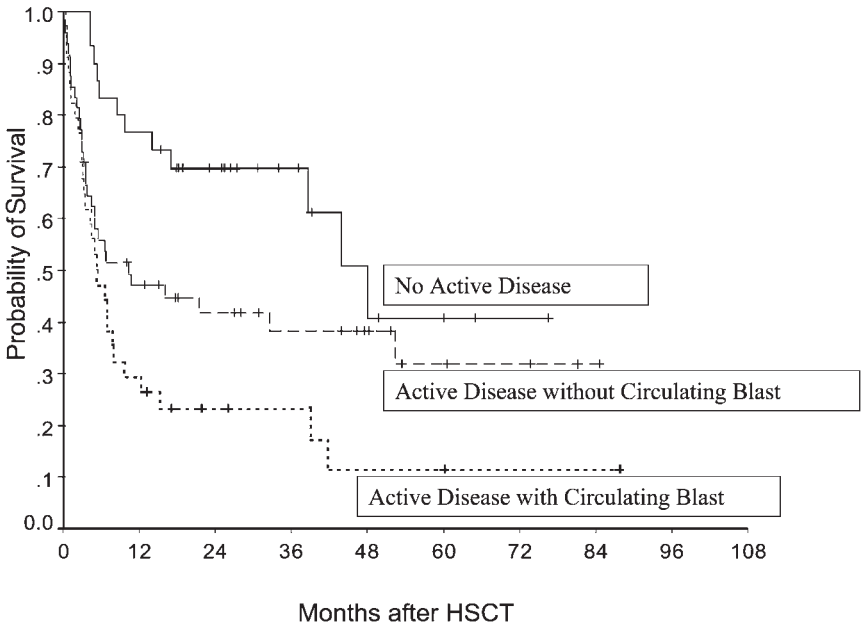
Transplantation for Older Patients in Myeloid Malignancies: Myelodysplastic Syndrome and Acute Myelogenous Leukemia

Marcos J. de Lima, MD

Acute myelogenous leukemia (AML) and myelodysplastic syndrome (MDS) are diseases of the elderly. Allogeneic hematopoietic stem cell transplantation offers the possibility of cure for these malignancies, but until recently its use was restricted to younger patients because of prohibitive treatment-related mortality. Improvements in supportive care and development of reduced-intensity preparative regimens have allowed patients in the sixth, seventh, and, to a lesser extent, eighth decades of life to be treated with allogeneic transplantation. There are, however, major obstacles to extending this form of treatment to older patients, including lack of promptly available donors, graft-versus-host disease (GVHD), delayed immune recovery, and the high prevalence of refractory and relapsed disease intrinsic to the natural history of these myeloid malignancies in the elderly.

Surveillance, epidemiology, and end results [1] data indicate that the general incidence rate of AML has been very stable over the last 30 years. However, there is a striking difference when this rate is corrected for age, reflecting the median age of these patients at diagnosis. The 5-year relative survival rate is improving, but there is a huge discrepancy in this survival rate as a function of age, with the main benefit occurring in patients younger than 50 years. A multiplicity of biological reasons contribute to this situation, which is further complicated in the case of MDS, a heterogeneous disease that has different prognoses according to stages and for which many new therapies are available. Among these therapies, unrelated donor hematopoietic stem cell transplantation with reduced-intensity preparative regimens has been shown to be an effective treatment for older and medically infirm patients. Wong et al [2] assessed the outcomes in 29 patients older than 54 years who received unrelated donor transplants for the treatment of advanced AML, and the results in this cohort of patients were comparable with those reported in younger patients with similarly advanced disease.



Overall survival by disease status at time of nonmyeloablative transplantation for patients older than 50 years with advanced or high-risk acute myelogenous leukemia/myelodysplastic syndrome.

Reduced-Intensity Regimens for MDS and AML: Special Considerations in Older Patients

Timing of transplantation is a singular process that is complicated by special considerations related to the disease itself and the treatment of older patients. Historical data on MDS show extremely high treatment-related mortality rates that essentially and statistically negate the benefit of the graft-versus-malignancy effect. The cytokine inflammatory cascade has a huge impact in older patients because of the increased likelihood of GVHD, which older patients are less likely to tolerate, and the fact that aging with disease, not necessarily aging itself, is a preinflammatory stage characterized by susceptibility to infections and less tolerance of steroid therapy.

These concerns provide the rationale for reduced-intensity transplantation regimens, but although nonmyeloablative or reduced-intensity transplantation would avoid some of these problems, the graft-versus-leukemia effect is an important aspect of this treatment strategy, and these diseases have lower intrinsic susceptibility to this effect.

The most commonly used nonmyeloablative regimens combine fludarabine, which induces potent immunosuppression and inhibits DNA damage repair, with total body irradiation or alkylating agents, such as melphalan.

We performed a 7-year follow-up study of nonmyeloablative transplantation with fludarabine and melphalan (FM). Participants were patients older than 50 years with advanced or high-risk AML/MDS who underwent matched related or unrelated donor transplantation with a comorbid condition that precluded the use of an ablative preparative regimen.

Most patients with active disease who underwent nonmyeloablative transplantation achieved complete engraftment on day 30, and 79% achieved a complete response, but grade II to IV acute GVHD occurred in approximately 40% and chronic GVHD in 60% of our patients. Within a follow-up period of approximately 30 months, 26% of our patients suffered disease progression. The likelihood of disease progression is high during the first 2 to 6 months posttreatment, especially in patients with active disease at the time of transplantation. Disease status at the time of transplantation was the most important risk factor for disease progression and determinant of survival (Figure). Most of the deaths occurred in the first 2 years, and later death was usually related to comorbidities, such as diabetes or stroke; but the most

important cause of death, even at 3 or 4 years posttransplantation, was chronic GVHD and delayed immune recovery. Another cause of death was iron overload related to previous transfusion treatment.

A major finding of this study and of a Seattle-based study [3] was that acute GVHD did not have a protective effect and, in fact, was a major cause of treatment failure in unrelated donor transplantation. Therefore, a better strategy for GVHD prophylaxis is needed for unrelated donor transplantation in older patients with MDS and AML.

Dose Intensity

Intensity of the preparative regimen is an important component of allogeneic transplantation for MDS or AML. We compared outcomes after a truly nonablative regimen (fludarabine, cytarabine, and idarubicin) and a more myelosuppressive, reduced-intensity regimen (FM) [4]. FM was significantly associated with a higher degree of donor cell engraftment, higher cumulative incidence of treatment-related mortality, and lower cumulative incidence of relapse-related mortality. In a multivariate analysis of patient- and treatment-related prognostic factors, progression-free survival was improved after FM for patients in complete remission (CR) at transplantation and for those with intermediate-risk cytogenetics. Survival was improved for patients in CR at transplantation. In conclusion, FM provided better disease control, although at a cost of increased transplantation-related mortality and morbidity.

Who Should Undergo Transplantation?

The American Society for Blood and Marrow Transplantation and the National Marrow Donor Program recommend the following conditions as indications for transplant consultation in AML and MDS patients [5]:

- High-risk AML
- Antecedent hematologic disorder
- Treatment-related leukemia
- Induction failure
- First CR with poor cytogenetics
- Second and later CRs
- MDS International Prognostic Scoring System risk category intermediate 1, 2, or high (includes >5% blasts, cytogenetics other than 5q- or diploid, >1 lineage cytopenia)

These recommendations do not include any guidelines related to age, but for these diseases the current results of any available therapy are dismal. Assessment tools such as the Charlson Comorbidity Index are available for scoring pretransplantation comorbidities that are predictive of nonrelapse mortality and survival and may be useful in decision making [6]. In general, elderly patients should be included in clinical trials whenever possible. Similarly, in regard to the timing of transplantation, most studies have been done with fairly young patient cohorts with only sibling donors, which are less likely to be available to older patients, so again the most important recommendation is that older patients should be included in clinical trials so that more data are available on timing of transplantation in these patients.

Conclusions

Reduced-intensity regimens have expanded the use of allograft to older patients. Older patients benefit from the highest dose intensity that can be delivered, but assignment to regimen should take into account comorbidities, age, diagnosis, disease stage, and the source of stem cells. Although it can now be said definitively that age, per se, should not be a contraindication to transplantation, in the context of MDS it is very hard to make clear-cut recommendations and to define the exact role of transplantation. The situation promises to become clearer with ongoing improvements in preparative regimens and GVHD prophylaxis. There is also a lot of hope in posttransplantation cancer vaccines that could help consolidate treatment responses. It is important for physicians to consider incorporating new agents as they become available, especially for patients who undergo transplantation with active disease, and to involve older patients in clinical trials as much as possible.

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Transplantation for the Older Patient: More Choices for Improving Outcomes

CME Assessment Test

1. **Which of the following is true regarding the aging patient population?**
   A. Certain cytokines are demonstrably reduced with age, including interleukin (IL)-2 and IL-12, whereas others (including IL-6 and IL-10) increase.
   B. Frailty is a normal part of the aging process and occurs in all individuals.
   C. Of all the people over the age of 65, about half living in the community but fewer than half rate their health as excellent or good.
   D. All of the above.
2. **Which of the following is true of age-associated anemia?**
   A. In most cases the mechanism for age-associated anemia can be easily determined.
   B. Older individuals with high levels of IL-6 are most likely to have lower erythropoietin and a diminished marrow response to anemia.
   C. Anemia in the elderly is not associated with inflammatory cytokines.
   D. All of the above.
3. **Which of the following is true of cancer in older patients?**
   A. Treatment outcomes are, in general, comparable in younger versus older patients receiving nonemergency surgery, elective radiation, and even chemotherapy.
   B. There is a bias against using aggressive treatments in older patients, but this bias usually comes from physicians, nurses, and family, and less frequently from the patients themselves.
   C. Although older people are more likely to have cancer, cancer may be less malignant in older people.
   D. All of the above.
4. **Which of the following is true of autologous versus allogeneic transplantation?**
   A. The major concern in allogeneic transplantation is disease recurrence.
   B. Allogeneic transplantation offers the advantages of high doses of chemotherapy or radiation along with the graft-versus-leukemia or graft-versus-tumor factor.
   C. The type of disease being treated is not an important factor in choosing the mode of treatment.
   D. All of the above.
5. **Which of the following is true regarding the choice between myoablative and nonmyeloablative treatment in older patients?**
   A. The choice between nonmyeloablative and myeloablative transplantation should be individualized and not made simply on the basis of age.
   B. Advanced age has never been identified as an adverse prognostic factor for patients undergoing myeloablative allogeneic transplantation.
   C. Treatment-related mortality rates are increased after nonmyeloablative transplantation, and risk of relapse is increased after myeloblative transplantation.
   D. All of the above.
6. **Which of the following are advantages of the use of nonmyeloablative treatment in older patients?**
   A. Less intense preparative regimens are less toxic and are better tolerated by older patients.
   B. Nonmyeloablative transplantation may be associated with less acute GVHD.
   C. In terms of cost comparison, across the board the nonmyeloablative transplantation is associated with lower costs.
   D. All of the above.
7. **Which of the following is true of hematopoietic stem cell transplantation as a therapy for low-grade B-cell malignancies?**
   A. This strategy is most commonly used in older patients even though these diseases are more common in younger patients.
   B. Transplantation-related toxicity is not a factor that excludes patients from this treatment.
   C. These disorders share a strong sensitivity to the graft-versus-tumor effect associated with allogeneic transplantation.
   D. All of the above.
8. **Which of the following effects are attributable to graft-versus-tumor effects in transplantation for low-grade B-cell malignancies?**
   A. Relapse rates are higher in patients who receive transplants from an identical twin than in patients who receive transplants from HLA-matched siblings.
   B. Donor lymphocyte infusions are sometimes effective for treating relapse.
   C. In patients who do relapse, disease regression sometimes occurs with the withdrawal of immunosuppression.
   D. All of the above.
9. **Which of the following is true of MDS and AML treatment in older individuals?**
   A. In general, elderly patients should go on clinical trials whenever possible.
   B. Older patients are less likely to have sibling donors for transplantation.
   C. Unrelated-donor hematopoietic stem cell transplantation with reduced-intensity preparative regimens has been shown to be an effective treatment for older and medically infirm patients.
   D. All of the above.
10. **Which of the following is NOT considered by the American Society for Blood and Marrow Transplantation/National Marrow Donor Program to be an indication for transplant consultation in AML and MDS patients?**
    A. Treatment-related leukemia.
    B. Second and later complete remissions.
    C. Patient age younger than 60 years.
    D. All of the above.

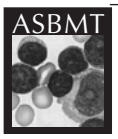
CME Assessment Test Answer Sheet

Release Date: March 31, 2006 **Last Review Date: March 31, 2006** **Expiration Date: March 31, 2007**

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 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 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
Educational objectives were achieved.	1	2	3	4	5
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.

Would you benefit from additional CME programs on this topic? Yes No

I have read these articles on the transplantation for the older patient, 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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