Blood and Marrow TRANSPLANTATION

REVIEWS

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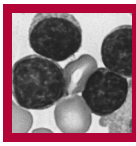

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The Malaise of Myelodysplasia

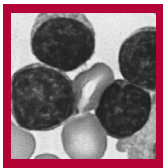
John R. Wingard, MD, Editor

Management of myelodysplastic syndrome has been disappointing for years. The mainstay approach was only supportive care. A malaise settled all around.

This issue presents a transcript of a symposium that addresses the topic of new therapies for myelodysplastic syndrome. This symposium was presented at the 2006 BMT Tandem Meetings in Honolulu, Hawaii. In the first presentation, Dr. Lewis R. Silverman describes the various types of myelodysplastic syndrome and provides insight into pathophysiology and therapeutic implications that research in recent years has uncovered. In the second presentation, Dr. Vinod Parameswaran notes that while allogeneic hematopoietic cell transplantation is curative, the obstacles in the path to transplantation are many. In the third presentation, Drs. Richard Champlin and Marcos de Lima describe new transplantation strategies with reduced-intensity preparative regimens and exploratory posttransplantation therapies in patients at high risk for relapse.

Today there are new Food and Drug Administration–cleared therapies, and novel agents are on the horizon. True progress has been small to date, but with the number of new therapies and new classes of agents undergoing study, the future is hopeful.

Will the malaise of myelodysplasia abate? Only time will tell. For now, there is considerably more hope than in the past.



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New Guidelines Help Health Professionals Recognize and Manage Late Complications

A consensus panel has developed recommendations for health care providers on prevention, screening, and management of late complications after autologous and allogeneic hematopoietic cell transplantation (HCT). The recommendations are published in the February 2006 issue of *Biology of Blood and Marrow Transplantation*.

With improvements in HCT technology, larger numbers of transplant recipients survive free of the disease for which they received transplantation. However, there are late complications that can cause substantial morbidity. Many survivors are no longer under the care of transplantation centers, and many community health care providers may be unfamiliar with health matters relevant to HCT.

The Center for International Blood and Marrow Transplant Research (CIBMTR), European Group for Blood and Marrow Transplantation (EBMT), and American Society for Blood and Marrow Transplantation (ASBMT) developed the recommendations to offer health care providers suggested screening and prevention practices for autologous and allogeneic HCT survivors.

Two New Investigators Win BBMT Editorial Awards

Two medical scientists are the recipients of editorial awards for new investigators for their articles published this past year in *Biology of Blood and Marrow Transplantation*. Each is the recipient of a $5,000 prize.

Swati Bhattacharyya, PhD, of the University of California San Francisco Children's Hospital, is winner of the Ernest McCulloch & James Till Award for best basic science article by a new investigator. The award is supported by an education grant from StemCell Technologies Inc.

Her article, published in the September 2005 issue, was "B7.2$^{-/-}$ Mature Dendritic Cells Generate T-Helper 2 and Regulatory T Donor Cells in Fetal Mice after In Utero Allogeneic Bone Marrow Transplantation."

Marie Jaksch, PhD, of Karolinska University Hospital, Huddinge, Sweden, is recipient of the George Santos Award for best clinical science article by a new investigator. The award is supported by an education grant from StemSoft Software Inc.

Her article, published in the April 2005 issue, was "Increased Gene Expression of Chemokine Receptors Is Correlated with Acute Graft-versus-Host Disease after Allogeneic Stem Cell Transplantation."

The awards were presented by *BBMT* Editor-in-Chief Robert Korngold, PhD, and representatives of StemSoft Software and StemCell Technologies. Selection of the winning articles was by the *BBMT* Editorial Board and the ASBMT Publications Committee.

H. Lee Moffitt Physician-Scientist Receives ASBMT/PDL New Investigator Award

An assistant professor at the University of South Florida's H. Lee Moffitt Cancer Center & Research Institute is the recipient of a New Investigator Award from ASBMT and PDL BioPharma.

Xue-Zhong Yu, MD, is a member of the cancer center's Experimental Therapeutics Department. His research concerns the function of Tregs and T-effector cells. The $50,000 award, payable over a two-year term, is supported by a grant from PDL BioPharma, Inc.

Dr. Yu will explore the molecular mechanisms and possible clinical implications of CD4+CD25+ T-regulatory cells (Tregs), a subset of T-cells that can modulate alloresponses and possess great potential as an immunotherapy in bone marrow transplantation.

He plans a series of studies on the function of Tregs and T-effector cells (Teffs), with the goal of understanding the ways in which the CD28 receptor and inducible T-cell co-stimulator (ICOS) control T-cell responses to alloantigen. Both CD28 and ICOS have been found to influence the activation and function of Teffs as well as development and function of Tregs.

The suppressive activity of Tregs lacking CD28 or ICOS will be tested in vitro and in mouse models of graft-versus-host disease (GvHD). The effects of CD28 and ICOS on regulatory and conventional T-cells will be examined as well. The findings will aid in understanding the mechanisms by which these costimulatory molecules affect the outcomes of GvHD. Dr. Yu said that he hopes his research will contribute to new approaches to controlling donor T-cell induced GvHD after allogeneic bone marrow transplantation, while preserving the graft-versus-tumor effect.

Six Abstracts Chosen Best of BMT Tandem Meetings

Six of the 510 abstracts accepted for the 2006 BMT Tandem Meetings were selected for awards by the abstract review committees. Recipients of the ASBMT Best Abstract Awards for Basic Science Research were:

- Michael Albert, MD, Dr. von Haunersches Kinderspital, Munich, Germany—*Antigen-Dependent Suppression of Graft-versus-Host Disease by Foxp3-Induced Regulatory T-Cells in Transplantation*
- Lia Perez, MD, H. Lee Moffitt Cancer Center, Tampa—*Microenvironment Confers Resistance to TRAIL-Mediated Apoptosis*
- Seitaro Terakura, MD, Nagoya University Graduate School of Medicine, Japan—*A Single Minor Histocompatibility Antigen AELLNIPLY Encoded by UGT2B17 Is Presented by HLA-A*2902, B*4402 and B*4403*

Each received a $1,000 prize. The basic research awards are supported by a grant from Nature Publishing Group.

Recipients of the CIBMTR Best Abstract Awards for Clinical Research were:

- Catherine Bollard, MD, Baylor College of Medicine, Houston—*The Clinical Use of LMP2-Specific Cytotoxic T-Lymphocytes for the Treatment of Relapsed EBV +ve Hodgkin Disease and Non-Hodgkin Lymphoma*
- George McDonald, MD, Fred Hutchinson Cancer Research Center, Seattle—*Oral Beclomethasone Dipropionate for Gastrointestinal GvHD: a Corticosteroid-Sparing Treatment with Improved Survival at Day +200*
- Olle Ringdén, MD, PhD, Karolinska University Hospital, Stockholm—*Mesenchymal Stem Cells for Treatment of Severe Acute Graft-versus-Host Disease*

Each also received a $1,000 prize. The clinical research awards are supported by a grant from Gambro BCT.

BMT Tandem Meetings Education Book Available

A limited number of copies of the *Education Book* for the 2006 BMT Tandem Meetings are available to those unable to attend the meetings for use in training programs or as an introduction or update on the field of hematopoietic stem cell transplantation and cellular therapy.

The book is edited by Claudio Anasetti, MD, and originally was published as a supplement to *Biology of Blood and Marrow Transplantation*. Articles include:

- T-Cell Trafficking and Homing—*Robert Sackstein, MD, PhD*
- T-Cell Therapy—*Stanley Riddell, MD*
- Cancer Vaccines—*Jeffrey Molldrem, MD*
- Genomic Polymorphism—*Charles Mullighan, MD, PhD*
- Advances in HLA—*Dennis Confer, MD*
- Clinical Use of Cord Blood Cells—*Vanderson Rocha, MD, PhD*
- Genomics and BMT in Lymphoma—*Sandeep Dave, MD, MS*
- Treatments for Follicular Lymphoma—*Arnold Freedman, MD*
- Transplantation for FCL—*Ginna Laport, MD*
- Advances in Hodgkin's Disease—*Andreas Josting, PhD*
- Genomics and BMT in Myeloma—*John Shaughnessy, Jr., PhD*
- Biology and Treatment of Myeloma—*Patrizia Tosi, MD*
- Immune Reconstitution—*Kenneth Weinberg, MD*
- Infections and BMT—*Eric Pamer, MD*
- Biology of Aging—*William Ershler, MD*
- Nanotechnology: Basic Principles—*Prof. Warren Chan*
- Nanotechnology: Applications—*Carlo Montemagno, PhD*
- Analysis of Transplant Outcomes—*John Klein, PhD*

To purchase copies of the *Education Book* at $20 each, contact the Elsevier Customer Service Department and provide Order Code SXBB.

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ASBMT

Symposium Report

Blood and Marrow TRANSPLANTATION REVIEWS

Before and After Transplantation: Treatment Strategies for Patients with Myelodysplastic Syndromes

Adapted from a CME symposium presented at the American Society for Blood and Marrow Transplantation and the Center for International Blood and Marrow Transplant Research 2006 BMT Tandem Meetings on February 16, 2006, in Honolulu, Hawaii.
This program is supported by an unrestricted educational grant from Pharmion Corporation.

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

Lewis R. Silverman, MD, is a consultant for Novartis and Roche, and has received honoraria from Pharmion.

Vinod Parameswaran, MD, has received honoraria from Pharmion and MGI Pharma.

Richard E. Champlin, MD, has received honoraria from Celgene and Pharmion.

Marcos de Lima, MD, has received honoraria from Pharmion.

Needs Assessment

Myelodysplastic syndrome (MDS) is a relatively rare disease. There are approximately 15,000 diagnosed MDS cases in the United States, but many more may be undiagnosed. Education on the disease characteristics and available treatment options is needed by bone marrow transplantation physicians, who are often the first to diagnose MDS and are likely to treat MDS patients.

Target Audience

Physicians and allied health professionals specializing in blood and marrow diseases.

Learning Objectives

- Characterize the current state of MDS treatment, including stem cell transplantations as the only potential curative option.
- Compare current drug treatment options in elderly MDS patients with multiple comorbidities.
- Discuss the possible role of DNA methyltransferase inhibitors in reducing the risk category of MDS prior to transplantation in MDS patients awaiting a transplant match.
- Describe new therapies for posttransplantation treatment of patients with MDS

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Modulation of the Clone: Altering the Course of Myelodysplastic Syndrome

Lewis R. Silverman, MD

Myelodysplastic syndrome (MDS) is a clonal disorder that develops from a multipotent hematopoietic progenitor cell. Clinically the dominant manifestation is ineffective hematopoiesis with peripheral blood cytopenias leading to bone marrow failure. Infection and bleeding related to bone marrow failure syndrome are the cause of death in most patients with MDS. In approximately 35% to 40% of cases, MDS transforms to acute myeloid leukemia (AML).

There are estimated to be 15,000 to 25,000 new cases of MDS in the United States per year. MDS occurs predominantly in older patients, with a median patient age of approximately 65 years in most studies.

Hematopoietic stem cell transplantation is a treatment option for only 5% to 10% of the MDS population. Until recently, supportive care has been the standard of therapy for MDS. In the last year and a half, however, the United States Food and Drug Administration has approved 3 new drugs, azacitidine, lenalidomide, and decitabine, for treatment of MDS, and other promising new agents are being investigated.

MDS Classification

Accurate classification of MDS is imperative because it allows appropriately targeted treatment. Because of the variability of MDS, several systems of disease classification have been developed. The most commonly used systems are the French-American-British (FAB), the World Health Organization (WHO), and the International Prognostic Scoring System (IPSS).

The oldest MDS classification scheme, the FAB [1], is still used in MDS diagnosis but is being supplanted by the WHO classification. The FAB classification system distinguishes 5 subgroups of MDS on the basis of blast percentage, number of ringed sideroblasts, degree of monocytosis, and percentage of myeloblasts. One of the main features used to distinguish the FAB subtypes is the proportion of blast cells, immature precursors of granulocytes (myeloblasts) that do not normally appear in peripheral blood and can be recognized by their large size and primitive nuclei in the peripheral blood and/or bone marrow. The 5 FAB subtypes are:

- Refractory anemia (RA; <5% blasts)
- Refractory anemia with ringed sideroblasts (RARS)
- Chronic myelomonocytic leukemia (CMML)
- Refractory anemia with excess blasts (RAEB; 5%-20% blasts in the bone marrow)
- Refractory anemia with excess blasts in transformation (RAEB-t; 21%-29% blasts in the bone marrow)

MDS Categories of FAB Classification versus WHO Classification*

FAB	WHO
RA (<5% blasts)	RA
	Refractory cytopenia with multilineage dysplasia
	MDS-unclassified
	MDS with isolated del (5q)
RARS (<5% blasts plus >15% ringed blasts)	RARS
	Refractory cytopenias with multilineage dysplasia and ringed sideroblasts
RAEB (5-20% blasts)	RAEB-1 (5-9% blasts)
	RAEB-2 (10-19% blasts)
RAEB-t (21-30% blasts)	Acute myeloid leukemia (>20% blasts)

*FAB indicates French-American-British; WHO, World Health Organization; RA, refractory anemia; MDS, myelodysplastic syndrome; RARS, refractory anemia with ringed sideroblasts; RAEB, refractory anemia with excess blasts; RAEB-t, refractory anemia with excess blasts in transformation.

It is now proposed that the presence of >20% bone marrow blasts is diagnostic for acute myeloid leukemia (AML) in any of its forms. CMML, which was part of the original FAB classification scheme, is no longer included.

The WHO classification scheme, first reported in 1999 [2], formally incorporates the relationship of AML to MDS and modifies and expands the FAB classification scheme (Table). In particular, RAEB is subdivided into 2 groups on the basis of marrow blast percentage. The WHO classification eliminates the FAB subgroup of RAEB-t, lowering the marrow blast threshold for MDS-AML from 30% to 20%, and adds cytogenetically defined entities such as (del) 5q syndrome. The WHO MDS classification also specifies that unilineage anemia and erythroid dysplasia characterize the low-grade FAB subtypes, RA and RARS, and adds a new category, refractory cytopenia with multilineage dysplasia, for cases with l dysplastic feature involving more than the erythroid lineage.

The IPSS [3] (Figure 1) is a more deliberate prognostic scoring system that assigns point scores on the basis of diagnostic features. Total score values are grouped into 4 different risk categories (low, 0 points; intermediate [int]-1, 0.5-1 points; int-2, 1.5-2 points; and high, ≥2 points). IPSS low-risk MDS tends to have a more slowly evolving course, with a median time of survival of approximately 3.5 to 5 years and a low rate of transformation to AML. In contrast, IPSS high-risk MDS tends to have very short survival and rapid progression to AML.

MDS Pathophysiology

Numerous pathophysiological abnormalities have been identified in MDS. The vascular endothelial growth factor (VEGF) signaling pathway is altered so that VEGF has autocrine effects on the MDS clone and paracrine effects on the microenvironment, both enhancing MDS clone survival. In addition, the cytokine signaling pathway is impaired. Cells do not respond appropriately to erythropoietin even though the erythropoietin receptor number and binding affinity are normal in MDS patients, activation of Stat-5 signaling and the translation of the signal to the nucleus are impaired. This impairment is thought to lead to abnormalities in differentiation and may partly explain the accelerated apoptosis that

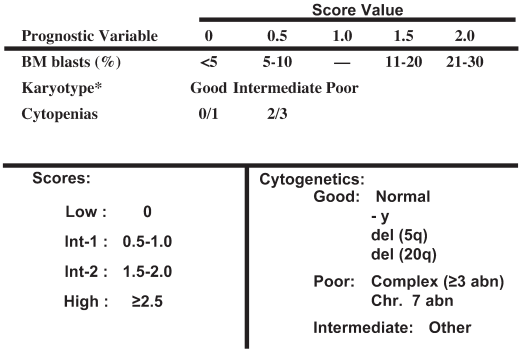

Figure 1. International Prognostic Scoring System score for myelodysplastic syndrome staging.

has been identified in MDS patients. This explains the ineffective hematopoiesis leading to hypercellular bone marrows and pancytopenia that occur in MDS.

The cellular microenvironment is also abnormal in MDS. Overproduction of tumor necrosis factor α, transforming growth factor β, interleukin 1β, and interferon γ, all of which are negative regulators of hematopoiesis, leads to decreased hematopoiesis in the bone marrow. DNA mutations also contribute to MDS, and cytogenetic abnormalities are found in approximately 50% of MDS patients.

Environmental factors that have been implicated as contributors to MDS pathology include benzene, chemotherapy, and radiation therapy. Cigarette smoking implicated in the cause of AML may also be a contributor, but this has yet to be confirmed.

Targeted Therapy for MDS

Despite all of the identifiable abnormalities in the signaling pathways and in the pathophysiology of MDS, a unifying abnormality has not been identified as a target for therapy. A generalized approach to MDS is to divide patients into 2 broad groups of lower-risk and higher-risk patients. For lower-risk patients there are a number of different options, including observation without therapy, cytokine treatment, and newer therapies such as lenalidomide, azacitidine, thalidomide, investigational agents, and bone marrow transplantation. In most cases intensive chemotherapy is not considered to be an appropriate option for low-risk patients. For higher-risk patients there are fewer choices, with azacitidine being the primary approach, followed by investigational treatments including stem cell transplantation, which has not been clearly demonstrated to benefit high-risk patients.

Lenalidomide Therapy in MDS

Lenalidomide was recently approved for patients with (del) 5q abnormalities who have IPSS low or int-1 risk disease and are red cell transfusion dependent. In recent clinical trials, patients with (del) 5q abnormalities became red cell transfusion independent after treatment with lenalidomide [4]. In a study in which MDS patients who were red cell transfusion dependent with low or intermediate-1 disease without (del) 5q abnormalities, 27% of patients became transfusion independent after treatment with lenalidomide [5]. Median duration of transfusion independence was approximately 53 weeks for patients with and 43 weeks for patients without the (del) 5q abnormality. Elimination of the 5q clone occurred in 44% of the 5q-patient population, and a reduction by 50% or more in the MDS clone was observed in an additional 24% of patients treated with lenalidomide. Further investigation is needed to determine whether the clone reappears in patients with recurrence of red cell transfusion dependency. The long-term significance of this finding also remains to be determined.

Differentiation Therapy in MDS

Differentiation therapy was first demonstrated by Charlotte Friend et al in the early 1970s [6] and has been updated with the observation that changes in cell differentiation or a malignant phenotype may be brought about in part through silencing of genes through effects on DNA methylation and changes in histone protein deacetylation. Suppression of normal regulatory processes within the cell can lead to tumor emergence, resistance, and progression. These recurring changes occur at a functional level, not through genetic mutations or cytogenetic abnormalities but through epigenetic silencing. These represent functional changes that can be reversed, leading to gene reexpression. The agents that can do this are the hypomethylating agents (azacitidine and decitabine) and the histone deacetylase (HDAC) inhibitors (vorinostat [SAHA], MS-275, valproic acid, depsipeptide, and MGCD0103). All of the HDAC inhibitors are investigational agents except valproic acid, an antiseizure drug that has been shown to have HDAC activity and is being investigated as a treatment for MDS and AML.

Within mammalian DNA, only cytidine residues are methylated. The methylated cytidine residues tend to cluster around the promoter region of genes in areas called CpG islands. When these areas are unmethylated, the promoter region can be accessed by transcription factors, leading to gene transcription and normal gene expression. Methylation through the action of DNA methyltransferases, however, can either bind methyl-binding proteins or directly block the action of transcription factors, which then no longer have access to the promoter region, leading to silencing of the gene and lack of transcription. Under the influence of hypomethylating agents, DNA methyltransferase is inhibited and hypermethylation can be reversed, thus allowing the transcription factor access to the promoter region, restoring transcription of the gene and reversing gene silencing (Figure 2).

In hematologic malignancies, a number of different genes have been identified as being hypermethylated. These genes may be involved in the dysregulation of cytokine signaling pathways and other growth pathways and are candidate genes for studying the effects of hypomethylating agents and investigating whether there is reversal of methylation and reexpression of these genes.

A study of azacitidine by the Cancer and Leukemia Group B [7,8] showed significant differences in complete remissions, partial remissions, and hematologic improvement categories in the azacitidine-treated group compared with the group receiving only supportive care, with overall response rates of 60% versus 5%. There was a significant reduction by 60% in the frequency of AML

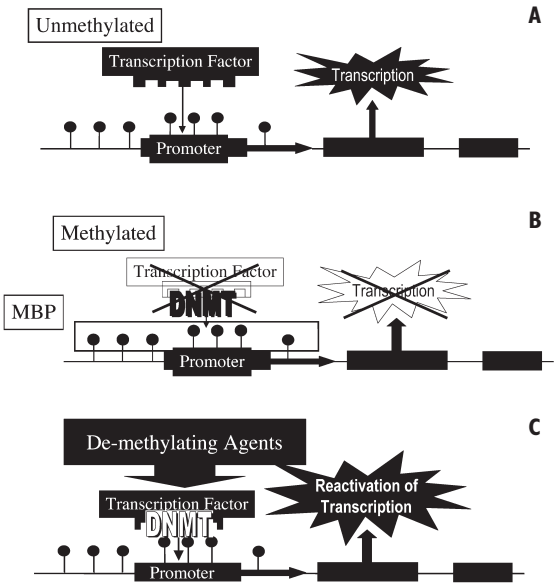

Figure 2. Functional control of gene transcription: methylation and gene silencing. A, In the functioning unmethylated gene, transcription factor binds to the promoter, resulting in gene activity (transcription). B, Aberrant methylation by DNA methyltransferase (DNMT) blocks the promoter region, thus silencing the gene by preventing transcription. C, The demethylating agent unblocks the promoter region, allowing binding of the transcription factor to the promoter region and reactivating normal gene transcription.

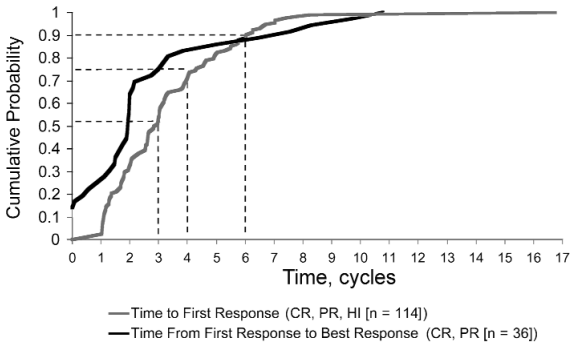

Figure 3. Times to first response and from first response to best response to azacitidine, according to International Working Group myelodysplastic syndrome response criteria. FISH indicates fluorescence in situ hybridization; CR, complete response; PR, partial response, HI, hematologic improvement.

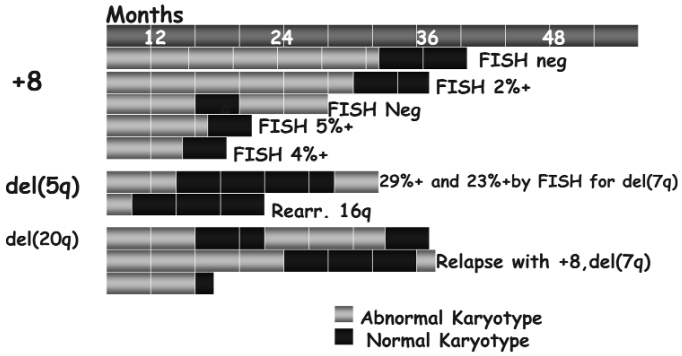

Figure 4. Time to normalize karyotype: reversal of an abnormal to normal karyotype in myelodysplastic syndrome patients treated with azacitidine.

transformation in patients treated with azacitidine. A number of different quality-of-life parameters, including physical functioning, fatigue, dyspnea, and overall quality of life, also showed improvement in the azacitidine-treated group [9]. Further analysis of transfusion data showed that for patients requiring red cell transfusions at baseline, 45% became red blood cell transfusion independent [10]. Of the responding patients, 86% of those treated initially with azacitidine and, after crossover, 93% of those treated become red cell transfusion independent.

In patients aged 65 years or older with higher-risk FAB subtypes, there was a statistically significant delayed time to AML transformation or death and a 53% reduction in risk of transformation to AML in patients treated with azacitidine. Survival was also significantly prolonged, the first demonstration of a survival advantage conferred by treatment in this MDS risk category [11].

Further analysis of patient response to azacitidine therapy after 4 cycles of therapy given in early studies suggests that some patients benefit from extended cycles of therapy. In 50% to 60% of patients treated with azacitidine, exacerbation of preexisting cytopenias occurred in the first 1 to 2 months of treatment but was not associated with increased infections, bleeding, or mortality [12]. Azacitidine was also effective in low-risk patients, with a 59% response rate including complete and partial remissions and hematologic improvement, in the lower-risk population.

We have consistently observed a slow time to response for azacitidine [10] (Figure 3). Our initial observation was a median time to response of approximately 4 months, and there is a subset of patient in whom a response takes 6 months or longer. These observations raise the question of what is the optimal duration of treatment before deciding that a patient is not responding to azacitidine.

The results of a phase III trial of the hypomethylating agent decitabine, which has received FDA approval, showed a significant delay in time to AML or death in high-risk MDS patients only [13].

Observation before and after treatment with hypomethylating agents reveals reduction in the methylation around the p15 promoter region. A clear-cut correlation of these changes in methylation with clinical response has been difficult to establish, however. Although methylation is certainly a biochemical marker for the action of hypomethylating agents, we are not certain that p15 is involved in the pathophysiology of MDS, so we may be looking at the wrong target, or there may be complex feedback involving other genes that are not being properly analyzed. Clearly further research is needed.

Other Effects of Hypomethylating Agents in MDS

In regard to the mechanism of action of azacitidine, investigation of the effect of azacitidine on the MDS clone indicates that although azacitidine treatment can eliminate the abnormal clone or lead to clonal evolution in some patients, the abnormal clone persists in many patients who respond to treatment. Patients with a persistent MDS clone who receive azacitidine treatment can have improvement in hematologic function up to and including complete normalization of the peripheral blood counts and elimination of blasts from the marrow and the peripheral blood, even though the MDS clone is still identified at the same level in their marrow. This suggests that azacitidine may be modulating the responsiveness of the MDS clone to a variety of signals. Another important finding is that cytogenetic analysis can be used to assess treatment response. Clinically apparent response such as improvement in marrow and peripheral blood counts may not be apparent for several months. Cytogenetic abnormalities may be eliminated by treatment, but in some patients this may take 36 to 40 months (Figure 4), again suggesting that there may be a benefit for ongoing maintenance treatment with azacitidine [14].

Another action of azacitidine is modulation of cytokine signaling, which could also modulate the trend in MDS toward apoptosis and poor differentiation, offering a possible explanation for the reduction in risk of leukemic transformation in patients treated with azacitidine.

Treatment Recommendations and Ongoing Research

In MDS patients with low-risk disease, marrow function helps define symptoms and transfusion need. Initially patients with well-conserved marrow function and low-risk disease may need only observation, but as their marrow function declines, cytokine, lenalidomide, azacitidine, or thalidomide may be effective agents. Stem cell transplantation, addressed in the next two articles, is also applicable in this setting.

For high-risk patients, data indicate that azacitidine should be the initial choice for treat-

ment. Treatment with decitabine and/or investigational agents in clinical studies may also be explored in those not benefiting from azacitidine, along with stem cell transplantation, which may be assuming a more important role in high-risk MDS patients, particularly when combined with new treatment agents.

The combination of HDAC inhibitors with hypomethylating agents in the laboratory produces synergy between the agents that will be tested in clinical trials. Trials of azacitidine combined with MS-275 or SAHA may demonstrate that HDAC inhibitors enhance the activity of azacitidine as a single treatment agent.

Azacitidine is being investigated for use as an induction agent in a reduced intensity nonmyeloablative strategy before stem cell transplantation in patients with intermediate to high-risk disease to see if up-front azacitidine treatment will improve event-free and overall survival in high risk MDS patients.

Conclusion

As we continue to develop treatment agents that can modify the course and behavior of low- and high-risk MDS, treatment decisions will focus on determining the best time to perform transplantation, the optimum duration of use of effective treatment agents before switching to potentially curative alternative therapies, and how to balance the risks versus the benefits of emerging therapies.

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The Bridge to Transplantation in Patients with Myelodysplastic Syndrome and Acute Myeloid Leukemia

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Despite advances in pharmacologic treatment of myelodysplastic syndrome (MDS), allogeneic stem cell transplantation remains the only curative therapy for this disease. Unfortunately, MDS patients face many barriers to transplantation. We must discover ways to bridge these barriers to maximize the success of transplantation in this patient population.

Factors Affecting Transplantation Outcomes in MDS Patients

MDS occurs primarily in older patients, few of whom are eligible for transplantation. Those who do undergo transplantation must face the fact that although there is hope for cure, the risk is high and the outcome remains dismal for most MDS patients. Age, disease stage, and conditioning regimen all affect the outcome from transplantation, both for HLA-identical sibling transplantation and unrelated donor transplantation (Table 1).

The optimal timing for transplantation is unknown, and there have been no evidence-based recommendations to date. A recently published analysis [1] indicated that transplantation during the early stages of disease is detrimental in low-risk MDS patients, and that improved outcomes are attained by delaying transplantation until disease progression (Figure). We have not discovered the exact indicators of disease progression that are related to these improved transplantation outcomes, however. In fact, one indicator of disease progression, worsening cytopenia, as occurs in AML transformation, has an adverse effect on the outcome of transplantation. Enhanced understanding of disease progression will also facilitate determination of the correct timing of transplantation in patients with high-risk MDS.

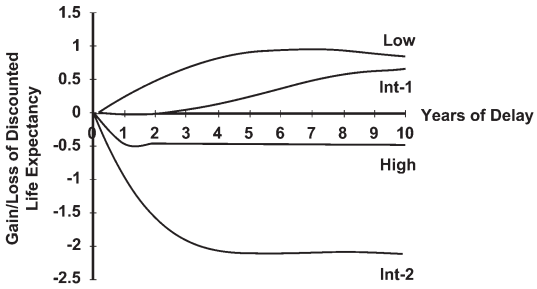
Addressing and Overcoming Clinical Barriers to Transplantation

For MDS patients for whom transplantation is deemed a suitable therapy, an optimum regimen for induction chemotherapy must be determined. We know that allogeneic transplantation is currently the only curative treat-

Table 1. Decision Analysis for Allogeneic Stem Cell Transplantation (SCT) for Myelodysplastic Syndrome (MDS)*

- Allogeneic SCT is currently the only curative therapy for MDS
- Majority of patients with MDS are >60 years old and few are candidates for myeloablative SCT
- SCT trials demonstrate long-term survival rates ranging from 25% to 70%
- Despite advances, considerable morbidity and mortality are associated with SCT
- Treatment-related and overall mortality are affected by:
  - Age
  - French-American-British subtype
  - Cytogenetic abnormalities
  - Conditioning regimen used
  - Duration of disease prior to SCT

*Based on [1].



Effect of delayed allogeneic stem cell transplantation in patients with myelodysplastic syndrome of different risk category. Int indicates intermediate. Used with permission from [1].

ment for MDS. Beyond that, we are not certain regarding the roles of autologous transplantation and maintenance therapy in MDS.

For allogeneic transplantation, sibling donors are available to only a small subset of patients; other sources include unrelated or partially mismatched donors and cord blood, but the use of these options in MDS patients has not been well investigated.

Ablative transplantation remains the cornerstone of curative therapy. Many MDS patients cannot tolerate a myeloablative preparative regimen, however. Although there is uncertainty as to how much improvement will be achieved by transplantation with a reduced-intensity conditioning regimen, more patients would be served with this approach because age, which is one of the adverse determinants of outcome, may not be a prohibiting factor for reduced-intensity conditioning. There is evidence that myeloablative radiation therapy should be avoided in MDS patients, but we have not determined the best reduced-intensity conditioning regimen.

For MDS patients who received transplants from HLA-identical siblings or alternative donors, a conditioning regimen of targeted busulfan and cyclophosphamide provided effective pretransplantation conditioning and was used successfully even in patients older than 60 years [2]. Although there was also considerable nonrelapse morbidity and mortality, nonrelapse mortality was reduced, and as a result, relapse-free survival rates were higher than those achieved with total-body irradiation conditioning regimens.

In patients with low-risk MDS, delayed transplantation is associated with better outcomes, but the effect of transplantation timing is less well understood in high-risk patients. In patients with high-risk disease with a high percentage of blasts in the bone marrow, proceeding quickly with induction chemotherapy would seem to be appropriate. Studies of this approach, however, have shown that chemotherapy treatment in these cases does not appear to impact overall survival [3], but persistence of blasts at the time of transplantation is associated with adverse outcomes [4]. This finding probably indicates that the persistent blasts are resistant to chemotherapy. Other options, such as modulating the disease clone with agents such as DNA methyltransferase inhibitors, may improve patient outcomes.

Results of a recent study in patients with advanced MDS, in which patients with an HLA-identical sibling donor underwent allogeneic transplantation and patients lacking a donor underwent autologous transplantation, showed no survival advantage for patients who received an HLA-identical allogeneic transplant [5]. These results, taken together with the finding that donor lymphocyte infusion is effective in some but not all MDS patients [6], indicate that some MDS is intrinsically resistant to adopted immunotherapy. We do not understand the mechanism of this resistance in MDS, but we do know that the bone marrow microenvironment plays a very important role in stem cell engraftment and differentiation. It has been shown in mouse models that nonclonal hematopoiesis can be achieved by reinfusion of MDS cells [7]. Perhaps the use of modalities of treatment that alter the marrow microenvironment or the disease clone itself may make the autologous transplantation option more feasible.

The MDS disease population is not a uniform one. Because MDS is mainly a disease of older people, various comorbidities are common and can have an adverse impact on transplantation outcomes. There are also ethnic variations in disease behavior and progression. For example, MDS in Asian patients appears to differ from MDS in Western patients [8,9], with MDS occurring at a younger age in Japanese and Chinese patients than in Western patients. In addition, Japanese patients tend to have more cytopenias but better prognosis and lower risk of leukemia, and Chinese patients have a lower incidence of chromosome 5 and 7 abnormalities. We are not certain how much of this variation is determined by genetic factors and how much by interaction of genetic factors with the environment. The same is true for the complications of transplantation, of which graft-versus-host disease (GVHD) remains an important one. White American, African-American, and Irish patients have significantly higher rates of acute GVHD and treatment-related mortality than do Japanese patients [10].

We know that in general patients who have GVHD have a lower risk of relapse because of the graft-versus-leukemia effect. GVHD incidence and outcomes vary, however, and this variation seems to be related to the distribution of single nucleotide polymorphisms in the population. This area of intense research focus for MDS and other diseases highlights the importance of genomic screening, which is not yet a standard approach for patients undergoing allogeneic stem cell transplantation. The introduction of more complex factors such as these into pretransplantation evaluation will impact the statistical models used to analyze study results.

Other Barriers to Transplantation

In addition to the biological disease aspects that are intrinsic to the patient and the donor, external cultural, environmental, and psychosocial factors can prove to be considerable barriers to transplantation. In the United States, Hispanic patients have worse outcomes from allogeneic transplantation than do white patients [11]. We are not certain how much of this difference is related to genetics and how much is due to comorbidity and socioeconomic status.

In culturally and ethnically diverse communities, medical underservice continues to be a social issue, exacerbated by disparities in health literacy and cultural competency. In the United States, 20% of the population resides in areas of physician shortage and poor health service access, and in these regions it is difficult for patients to benefit from available technology because they are less likely to have access to clinical research trials, which offer the best treatment outcomes for MDS patients. Because of the importance of adhering to the tenets of clinical research, understanding of the consent form is an important criterion for patient participation. According to a National Adult Literacy survey, a significant proportion of individuals find it difficult to understand the medical information that is provided. This is another important barrier that has to be overcome.

The National Marrow Donor Program has studied non-HLA barriers to transplantation in eligible patients who have access to treatment [12] (Table 2). Such patients may be prevented

Table 2. Non-HLA Barriers to Transplantation*

- 25% of donor searches at the NMDP run into non-HLA barriers
  - Patient died
  - Patient condition worsened/search took too long
  - Financial issues
  - No suitable donors
  - Other
- 20% of the searches in the United States stop because they are not in the patient's best interest
  - Treatment alternative
  - Physician decision
  - Patient stable
  - Patient/family decision

*Determined by the National Marrow Donor Program (NMDP) [12].

from undergoing transplantation because of death, worsening condition, financial issues related to insurance company approval for treatment, or physician decisions. Even in the best treatment centers, when patients are eligible for transplantation and an HLA identical donor is available, only approximately one fourth of them undergo transplantation.

Treatment center availability also affects access to transplantation. Not all patient communities are served by large transplantation centers. Numerous smaller transplantation centers perform 20 to 60 transplantations a year, and it is important to determine whether transplantation outcomes within these centers are uniform and comparable to those in large centers. Loberiza et al have shown that outcome differences related to treatment setting were less significant for autologous transplantation, but for allogeneic transplantation the day-100 mortality rates were lower in settings with larger physician:patient ratios and increased physician commitment as reflected by taking after-hours calls [13].

Donor selection is a more important issue in the older MDS patient population than in younger patients because older patients are likely to have older donors with comorbidities such as occult malignancies and autoimmune diseases that can be transmitted to the patient. We do not routinely perform malignancy screening in donor populations, but perhaps this procedure should be considered in treating patients with MDS who have older donors.

Conclusions

To achieve successful transplantation for MDS, patients and their health care providers must overcome many barriers. Although the situation might seem overwhelming for a disease as complex as MDS, recent achievements in MDS have created opportunities that offer hope for greater success in bridging the barriers to transplantation.

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Maintenance Therapy after Allogeneic Stem Cell Transplantation for Myelodysplastic Syndrome and Acute Myeloid Leukemia

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Marcos de Lima, MD

Myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) are primarily diseases of older persons. Because transplantation treatment approaches have historically focused on younger patients, little progress has been made in treating the largest group of MDS-AML patients. Now research is focused on optimization of transplantation treatment of AML and MDS, exploring novel treatment strategies and ways of improving the existing standard of care for patients of all ages, including the older patients who make up the bulk of the MDS-AML patient population.

Treatment results have improved in younger patients but not in elderly patients. From the 1970s to the 1990s, median survival of patients improved overall, but most of this improvement was in younger patients. A comparison of patients younger than 65 years with patients aged 65 years and older [1] showed that survival had not improved in the 65 and older group, the group that would most benefit from advances in therapy. Long-term survival in patients older than 55 years is 10% to 12% [2]. Poor outcomes in older patients are related to frailty and comorbid medical conditions that make them less able than younger patients to tolerate high-dose intensive treatments [2,3]. In addition, older patients have a higher prevalence of poor

prognostic features such as high-risk cytogenetic abnormalities.

Effect of Transplantation Timing on Outcomes

At MD Anderson Cancer Center (MDACC), we observed lower relapse rates for patients in remission at the time of transplantation than for patients not in remission (Figure 1). Approximately two thirds of patients who undergo transplantation while not in remission suffer relapse posttransplantation, usually within the first 3 to 6 months after transplantation. On the basis of these findings, we sought to develop maintenance strategies for patients at high risk for relapse. Such strategies must be performed quickly after transplantation, because even in patients who undergo transplantation while in remission, relapses usually occur within the first year posttransplantation.

Novel Transplantation Strategies for Older MDS Patients

In older patients, nonmyeloablative regimens, for which dose intensity can be adjusted, are usually used instead of myeloablative preparative regimens, which use maximum dose intensity. MDACC researchers found that patients treated with reduced-intensity regimens that were myelosuppressive had better results than patients who received truly nonablative regimens [4]. In the reduced-intensity transplantation setting, patients given a regimen with increased myelosuppressive dose intensity had higher remission rates and longer remission durations.

Unfortunately, in patients with refractory disease, transplantation outcomes have shown little to no improvement since the 1970s [5]. Efforts to date to intensify preparative regimens for patients undergoing transplantation in relapse have been largely unsuccessful, often producing excessive toxicity without improvement in long-term survival. However, newly available treatment agents and strategies have led to promising results.

Fludarabine in Transplantation

Fludarabine is an important new drug in transplantation preparative regimens. It inhibits DNA repair and acts synergistically when given with an alkylating agent, inducing cytotoxicity and apoptosis.

The combination of fludarabine and the alkylating agent melphalan has been shown to be effective in the treatment of AML and MDS [6], and at MDACC we are developing a reduced-dose regimen of melphalan and fludarabine that may make allogeneic transplantation treatment possible for patients up to the age of 75.

We used melphalan and fludarabine in a transplantation population that included patients as old as 74 years. Most of the patients were not in remission; and approximately 25% were in first, second, or third remission. Other patients had suffered relapse or primary induction failure. At the time of transplantation approximately one half of the patients had active disease but with some response to chemotherapy. These patients did not have circulating blasts, but leukemia was still evident in the bone marrow. Thirty percent of patients had overt relapse with circulating blasts.

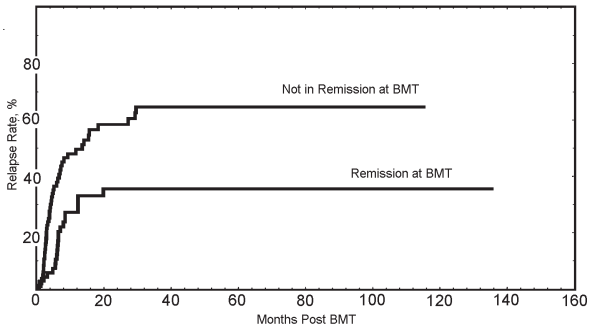

Figure 1. Rates of posttransplantation relapse according to disease status at the time of transplantation in myelodysplastic syndrome-acute myeloid leukemia patients treated at the MD Anderson Cancer Center, 1988-2000.

Relapse rates were highest in patients with active disease and circulating blasts. For patients with disease only in the bone marrow or no active disease, the relapse rate was approximately 20%. The reduced-intensity fludarabine combination produced results as good as those shown previously with total body irradiation but with much less toxicity, allowing treatment of a 74-year-old patient. Three-year survival rates were approximately 70% in patients who underwent transplantation in remission, approximately 40% in patients with active disease but without circulating blasts, and 20% to 25% in patients who underwent transplantation in overt relapse.

Gemtuzumab in Transplantation

At MDCC we have added gemtuzumab, a targeted therapy, to our core regimen of melphalan and fludarabine. Gemtuzumab is a humanized murine immunoglobulin G4 monoclonal antibody directed against the CD33 antigen and tagged with a toxin, calicheamycin. Gemtuzumab is an effective agent for treatment of patients with AML, even elderly patients. Although gemtuzumab can produce toxic myelosuppression, we hoped that addition of gemtuzumab to the melphalan and fludarabine regimen would improve the antitumor effects without increasing toxicity.

In our study, the gemtuzumab-melphalan-fludarabine combination was administered to 52 high-risk patients. Most of these patients had comorbid conditions and were not eligible for ablative regimens because of age, and 94% were not in remission at the time of transplantation. On the basis of phase I and II dose-finding studies to determine the maximum tolerated and optimal doses of gemtuzumab, we administered lower doses of gemtuzumab than would be used in other settings, but the low-dose gemtutzumab did reduce blasts counts before the administration of melphalan and fludarabine. Toxicity was a concern, particularly venoocclusive disease, but we observed only liver toxicity, which was reversible in all cases. Patients who received the gemtuzumab-melphalan-fludarabine combination had higher overall and disease-free survival rates (borderline significance) than did patients who received melphalan and fludarabine alone (Figure 2). Survival curves for patients undergoing this treatment indicated a delay in the initial high relapse rate that we would have seen with virtually every other regimen. Although the same, almost superimposable, curve of early failures from treatment-related complications or rapid relapse was present, this regimen at least made a minor impact on extending that forward. Thus the addition of gemtuzumab did not cause excessive toxicity and did have a modest benefit in these high-risk patients, increasing the long-term survival rate to 30% and overall survival rate to 40% compared to historical regimens and our experience, in which survival rates in transplantation patients with active disease were approximately 20%.

Posttransplantation Therapy

To delay or prevent disease recurrence, we introduced novel maintenance therapy with

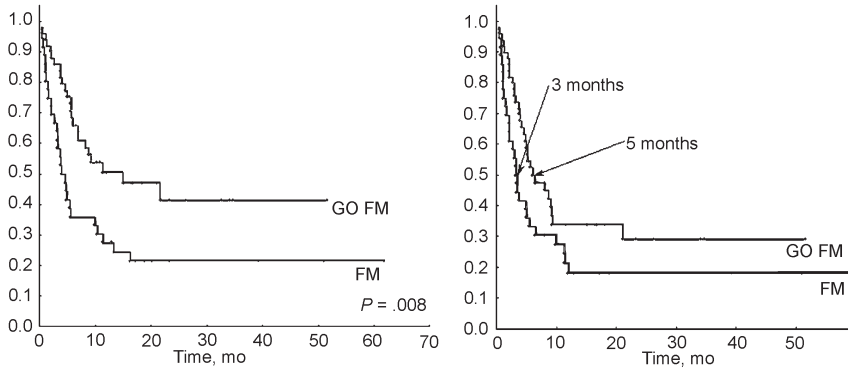

Figure 2. Overall survival (left) and disease-free survival (right) in patients treated with gemtuzumab-fludarabine-melphalan (GO FM) or fludarabine-melphalan (FM). The prolongation of event-free survival may provide time for posttransplantation interventions for relapse prevention.

azacitidine as a hypomethylating agent posttransplantation. Pioneering studies with decitabine, performed at our institution by Issa and coworkers, showed that administration of low doses of this hypomethylating agent, much less than needed for optimal myelosuppression, produced marked clinical benefit in patients with MDS, improving blood counts and delaying the time to progression [7]. The hypomethylating agents affect leukemia cells by inducing cell differentiation and expression of more mature markers. These agents also up-regulate class I and class II HLA molecules, potentially making cells more immunogenic.

We postulated that the use of posttransplantation therapy with azacitidine may enhance the graft-versus-leukemia effect by up-regulating leukemia-related antigens, thus making the cell more endogenic. Azacitidine may also prevent leukemia recurrence by acting on tumor suppressing genes and directly affecting leukemia stem cells to prolong remission and prevent or delay relapse, giving time for posttransplantation graft-versus-malignancy effects to occur. On the other hand, the same mechanisms might lead to adverse effects such as increased graft-versus-host disease, compromised graft function or immune recovery, or direct toxicity.

We are investigating this treatment in a new clinical trial, working from the hypothesis that posttransplantation treatment with azacitidine will decrease relapse rates after allogeneic transplantation performed after a preparative regimen of the gemtuzumab-melphalan-fludarabine combination tested in our prior studies. We are focusing on patients with advanced AML and MDS undergoing either HLA-identical sibling or unrelated donor transplantation. Azacitidine will be given to patients during the immediate posttransplantation period, when the bone marrow is very fragile and the patients are myelosuppressed and immunocompromised, with a high risk of infections and graft-versus-host disease. Thus we will investigate whether these patients can tolerate azacitidine and whether it affects the relapse rate compared to our historical data. We are just beginning to investigate posttransplantation maintenance for patients on this protocol, but we hope this novel approach may alter posttransplantation relapse rates.

Conclusions

Disease relapse remains the major cause of treatment failure after allogeneic transplantation in patients with relapsed or refractory MDS-AML. Novel more effective and tolerable preparative regimens are required to improve outcomes in these patients. Posttransplantation azacitidine treatment can potentially improve disease control by multiple mechanisms and thus shows promise as a treatment to reduce relapse rates. Ongoing research is needed to determine optimum dose and scheduling for azacitidine administration.

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Journal Watch

A scan of recent medical literature identified these articles of special importance in the science and clinical application of blood and marrow transplantation.

Adams GB, Chabner KT, Alley IR, et al: Stem cell engraftment at the endosteal niche is specified by the calcium-sensing receptor. Nature. 2006;439:599-603.

Hematopoietic stem cells (HSCs) are found near the endosteal bone surface under normal conditions, and migrate to this area soon after transplantation. The seven-transmembrane-spanning calcium-sensing receptor (CaR) may play a role in the mechanism by which HSCs respond to the high levels of calcium ions at the endosteal surface. The investigators assessed the expression of CaR on HSCs and its effects on stem cell responses in the endosteal niche.

Studies confirmed the expression of CaR on mouse HSCs. Primitive hematopoietic cells were detected in the circulation and the spleen of antenatal $CaR^{-/-}$ mice, but were sparse in the bone marrow. Fetal liver specimens showed normal numbers of $CaR^{-/-}$HSCs; proliferation, differentiation, migration, and homing to bone marrow were normal as well. However, these $CaR^{-/-}$ cells failed to localize normally to the endosteal niche. This defect was associated with lack of adhesion to collagen I, the major extracellular matrix protein of bone.

Calcium-sensing receptor plays a key role in the localization of HSCs in the endosteal niche, in response to the ionic mineral content in that microenvironment. The CaR likely plays a critical role in bone mineralization during development. In clinical stem cell transplantation, treatments addressed at CaR may be useful in promoting HSC engraftment to, or mobilization from, the endosteal niche.

Terlizzi SD, Zino E, Mazzi B, et al: Therapeutic and diagnostic applications of minor histocompatibility antigen HA-1 and HA-2 disparities in allogeneic hematopoietic stem cell transplantation: a survey of different populations. Biol Blood Marrow Transpl. 2006;12:95-101.

The minor histocompatibility antigens HA-1 and HA-2 have immunogenic variants, HA-1^H and HA-2^V, which elicit strong alloreactive T-cell responses restricted to HLA-A2; and their functionally silent nonimmunogenic variants, HA-1^R and HA-2^M. Although HA-1 and HA-2 are potential targets of immunotherapy, they have been useful in only limited numbers of patients undergoing hematopoietic stem cell transplantation (HSCT). This study explored the use of HA-1 and HA-2 disparity as a marker of host chimerism after allogeneic HSCT.

Typing for HA-1 and HA-2 polymorphisms was performed in a group of healthy blood donors from northern Italy, as well as in patients undergoing allogeneic HSCT for hematologic or solid malignancies. The HA-1^H allele was found in 29.3% of healthy individuals and the HA-1^R allele in 70.7%. The allelic frequencies of HA-2^V and HA-2^M were 83.7% and 16.3%, respectively. The results were similar in the cancer patients. Compared with other reported populations, the findings were consistent with the presence of a north-south gradient for the frequencies of HA-1 variants.

The results suggested that HA-1 could be used as a marker of host chimerism in 32.8% of Italian transplant recipients, while HA-2 could be used for this purpose in 23.5%. Disparities for these minor histocompatibility antigens might be useful for targeted immunotherapy in 10.7% and 1.1% of patients, respectively. Studies of bone marrow from patients in complete remission or recurrence indicated that HA-2 might be a useful surrogate for disease monitoring.

Genomic typing for HA-1 and HA-2 may prove to be a useful diagnostic and therapeutic tool in allogeneic HSCT. It may be particularly useful in donor selection, especially in patients with hematologic malignancies in whom no tumor-specific marker is identified. Because of the apparent north-south gradient in the HA-1^H variant, the HA-1 disparity will likely be of higher diagnostic value in southern populations.

Taieb J, Chaput N, Ménard C, et al: A novel dendritic cell subset involved in tumor surveillance. Nature Med. 2006;12: 214-219.

The tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) pathway, induced by interferon-γ (IFN-γ), plays a key role in tumor immune surveillance by natural killer (NK) cells in mice. A recent study of the antitumor effects of imatinib mesylate identified a new subset of dendritic cells (DCs), which produced high levels of IFN-γ and killed tumor cells via the TRAIL pathway. Further experiments were performed to characterize these IFN-γ-producing killer DCs (IKDCs).

Combination therapy with imatinib mesylate and interleukin-12 did not significantly increase the population of classical, CD3–B220–$NK1.1^+$ cells. Instead, 72% of tumor-infiltrating cells were atypical $B220^+NK1.1^+$ DCs, expressing NK cell-surface molecules. Even in contact with tumor cells not recognized by NK cells, these $B220^+NK1.1^+$ DCs produced high levels of IFN-γ and killed tumor cells via a predominantly TRAIL-dependent pathway. In adoptive transfer experiments, IKDCs prevented tumor outgrowth in effector-deprived *Rag2*$^{-/-}$*Il2rg*$^{-/-}$ mice, while classical NK cells did not.

The IKDCs evaluated in this study appear to be a phenotypically and functionally unique set of cells that play a key role in the innate antitumor response. This new DC subset may prove useful in cancer treatment, if it can be used to trigger tumor cell apoptosis via the TRAIL pathway. Human studies are needed to evaluate the role of IKDCs in tumor immune surveillance and their potential use in immunotherapy.

Janssens S, Dubois C, Bogaert J, et al: Autologous bone marrow-derived stem-cell transfer in patients with ST-segment elevation myocardial infarction: double-blind, randomised controlled trial. Lancet. 2006; 367:113-121.

Left ventricular remodeling and dysfunction limit the benefits of early coronary reperfusion in patients with ST-elevation myocardial infarction (STEMI). Nonrandomized trials have suggested that infusing autologous bone marrow-derived stem cells (BMSCs) into the infarct-related artery may promote functional recovery. A randomized, placebo-controlled trial was performed to evaluate the benefits of autologous BMSC transfer after myocardial infarction.

The study included 67 patients undergoing successful percutaneous coronary intervention with reperfusion after STEMI. The next day, bone marrow was harvested from each patient. Patients were randomly assigned to undergo coronary artery infusion of autologous BMSCs or placebo infusion; both groups received optimal medical care. The main outcome of interest was change in left ventricular ejection fraction at 4 months' follow-up.

Mean global ejection fraction increased from 46.9% to 49.1% in the BMSC group and from 48.5% to 51.8% in the placebo group—a nonsignificant difference. There was a significant difference in infarct size, with a treatment effect of 28% favoring BMSC infusion. Patients receiving autologous BMSCs also had better recovery of regional systolic function. Serial 1-[^{11}C]acetate positron emission tomography

scans showed comparable increases in myocardial perfusion and oxidative metabolism. There were no complications of BMSC infusion.

For patients with STEMI undergoing coronary reperfusion, autologous BMSC infusion does not improve left ventricular function, compared with placebo infusion. The observed changes in myocardial infarct size and regional left ventricular function suggest an effect on infarct remodeling, the clinical significance of which is unknown. Further study is warranted, including investigation of cell transfer conditions and patient selection criteria.

Tallman MS, Pérez WS, Lazarus HM, et al: Pretransplantation consolidation chemotherapy decreases leukemia relapse after autologous blood and bone marrow transplants for acute myelogenous leukemia in first remission. Biol Blood Marrow Transpl. 2006; 12:204-216.

High-dose cytarabine consolidation chemotherapy is commonly given before autologous hematopoietic stem cell transplantation for acute myelogenous leukemia (AML). However, the true benefits and risks of this approach are uncertain. The effects of high-dose and standard-dose consolidation chemotherapy on the outcomes of autotransplantation for AML in first remission were evaluated using registry data.

The Autologous Blood and Marrow Transplant Registry was used to identify three groups of patients undergoing autotransplantation for AML in first remission. The outcomes of 146 patients did not receive consolidation chemotherapy were compared with those of 244 patients receiving standard-dose consolidation therapy, less than 1 g/m^2 cytarabine; and 249 patients receiving high-dose consolidation therapy, 1 to 3 g/m^2 cytarabine.

There were no significant differences in 1-year transplant-related mortality. Five-year outcomes were better for patients receiving consolidation chemotherapy. Five-year relapse rate was 48% for patients not receiving consolidation therapy, compared to 35% with standard-dose and 40% with high-dose cytarabine. Five-year freedom from leukemia was 39%, 53%, and 48%, respectively.

Five-year overall survival was 42% without consolidation therapy, 59% with standard-dose cytarabine, and 54% with high-dose cytarabine. Number of treatment cycles had no effect on outcome—most patients received one or two courses.

For patients with AML treated with autotransplantation in first remission, long-term relapse and treatment failure rates are reduced with pretransplantation consolidation chemotherapy. Standard-dose and high-dose cytarabine yield similar outcomes. Although prospective studies are indicated, consolidation chemotherapy is recommended before autotransplantation for AML in first remission.

Collin MP, Hart DNJ, Jackson GH, et al: The fate of human Langerhans cells in hematopoietic stem cell transplantation. J Exp Med. 2006;203:27-33.

Along with other antigen-presenting cells, Langerhans cells are thought to be involved in initiating the graft-versus-host response after allogeneic hematopoietic stem cell transplantation. Recent evidence suggests that Langerhans cells may play a specific role in the biology of graft-versus-host disease (GVHD), separate from that of other peripheral myeloid-derived cells. This study examined the effects of modern conditioning regimens on human Langerhans cells, including their survival and reconstitution after transplantation.

Skin biopsy specimens were obtained from transplant recipients who had undergone full- or reduced-intensity conditioning regimens. Confocal microscopy was performed to examine epidermal sheets prepared from these specimens. On day 0, the full-intensity transplant regimen was associated with greater depletion of Langerhans cells than the reduced-intensity regimen. However, the low cell density levels were similar between groups, reached at 2 to 3 weeks after transplantation.

In patients without GVHD, Langerhans cell density returned to pretransplant values within 40 days. In contrast, for those with GVHD, Langerhans cell density remained depressed beyond 100 days. Donor chimerism was reached within 40 days in 97% of patients undergoing full-intensity transplantation, compared to 36.5% of those undergoing reduced-intensity transplantation. Chimerism was independent of blood myeloid engraftment. By 100 days, at least 90% Langerhans cell donor chimerism was reached in all cases, while 100% chimerism was reached in more than half of cases. There was an association between complete donor chimerism and the previous occurrence of acute cutaneous GVHD.

Current techniques of hematopoietic stem cell transplantation achieve high levels of Langerhans cell engraftment within 100 days. Langerhans cell recovery is slower in the presence of GVHD. Survival is similar for patients who do and do not achieve 100% chimerism. The association between complete chimerism and acute GVHD suggests that allogeneic T cells may promote Langerhans cell engraftment.

Reddy V, Winer AG, Eksioglu E, et al: Interleukin 12 is associated with reduced relapse without increased incidence of graft-versus-host disease after allogeneic hematopoietic stem cell transplantation. Biol Blood Marrow Transpl. 2005;11: 1014-1021.

The graft-versus-leukemia and graft-versus-host effects of allogeneic hematopoietic stem cell transplantation (HSCT) appear to be mediated via immune events. Animal models have suggested an antitumor effect of interleukin-12 (IL-12), although its importance in human transplantation is unclear. The association between circulating IL-12 and the clinical outcomes of HSCT was evaluated.

The prospective study included 134 patients undergoing allogeneic HSCT. Blood samples were obtained for IL-12 measurement before and on the day of transplantation and at 4, 7, and 14 days afterward. Groups of patients with low, medium, and high IL-12 levels were identified by cluster analysis, and clinical outcomes were compared between groups.

Levels of IL-12 peaked at 4 and 7 days after HSCT. Interleukin-12 was classified as low in 46 patients, medium in 49, and high in 25. Median IL-12 values in these groups were 2, 20.5, and 181 pg/mL, respectively. Post-transplant values were highest for patients with high baseline values.

On multivariate analysis, relapse rate was reduced for patients in the higher IL-12 groups. Adjusted hazard ratios were 0.27 for patients in the high-IL-12 group and 0.65 for those in the medium-IL-12 group, compared with the low-IL-12 group. Kaplan-Meier relapse rates at 500 days increased from 23.0% in the low group, to 40.3% in the medium group, to 48.8% in the high group. Interleukin-12 was unrelated to acute or chronic graft-versus-host disease.

Among allogeneic HSCT recipients, relapse-free survival is increased for patients with high IL-12 levels, with no associated increase in graft-versus-host disease. Patients with higher IL-12 levels before transplantation are more likely to have high levels of the same cytokine after transplantation, and thus may have better clinical outcomes. The role of IL-12 in prevention or treatment of relapse after allogeneic HSCT warrants further study.

Before and After Transplantation: Treatment Strategies for Patients with Myelodysplastic Syndromes

CME Assessment Test

1. **Which of the following classification systems is no longer considered to be useful for characterizing MDS and planning treatment?**
   A. French-American-British (FBS).
   B. World Health Organization (WHO).
   C. International Prognostic Scoring System (IPSS).
   D. None of the above.

2. **Which of the following is true of lenalidomide therapy in MDS?**
   A. This treatment is equally effective in MDS patients with and without 5q abnormalities.
   B. Lenalidomide treatment has resulted in transfusion independence but not elimination of the 5q clone.
   C. In patients in whom the 5q clone is eliminated, further study is needed to determine whether it will reappear after discontinuation of treatment.
   D. All of the above.

3. **Which of the following is true of targeted therapy for MDS?**
   A. Observation without therapy is never an appropriate option.
   B. Azacitidine is recommended as a primary approach to therapy in high-risk patients.
   C. Intensive chemotherapy in low-risk patients is usually appropriate because it delays transformation to higher-risk disease.
   D. All of the above.

4. **Which of the following effects of hypomethylating agents have been observed in MDS patients?**
   A. Improvement in marrow and peripheral blood counts.
   B. Elimination of blasts from the marrow and the peripheral blood, even though the MDS clone is still identified at the same level in the bone marrow.
   C. Elimination of trisomy 8 or other abnormalities of deletion 5q or deletion 20.
   D. All of the above.

5. **Which of the following is true regarding the effect of remission status on treatment outcomes in MDS patients?**
   A. Relapse rates are the same for patients in remission and for patients not in remission at the time of transplantation.
   B.Treatment of patients in relapse often produces excessive toxicity without improvement in long-term survival.
   C. Intensification of preparative regimens in patients undergoing transplantation in relapse greatly reduces the risk for relapse.
   D. All of the above.

6. **Which of the following is true regarding the use of fludarabine in patients undergoing transplantation treatment for MDS?**
   A. Fludarabine inhibits DNA repair and acts synergistically when given with an alkylating agent, inducing cytotoxicity and apoptosis.
   B. The combination of fludarabine and the alkylating agent melphalan has been shown to be effective in the treatment of AML and MDS.
   C. A reduced-dose regimen of melphalan and fludarabine that may make allogeneic transplantation treatment possible for patients as old as 75 years.
   D. All of the above.

7. **Which of the following is true regarding the use of gemtuzumab in patients undergoing transplantation treatment for MDS?**
   A. Gemtuzumab combined with melphalan and fludarabine was shown to have a modest benefit in high-risk patients.
   B. Like other regimens, gemtuzumab-melphalan-fludarabine failed to increase survival rates in MDS patients who were not in remission at the time of transplantation.
   C. Toxicity is not a concern with gemtuzumab treatment.
   D. All of the above.

8. **Which of the following is true regarding the effect of transplantation timing on treatment outcomes in MDS patients?**
   A. Evidence-based recommendations have been made for the optimal time for transplantation in the course of MDS.
   B. Because cytopenia worsens over time and has an adverse effect on outcomes, transplantation should be performed early in the disease course in all MDS cases.
   C. A recent analysis indicated that in low-risk MDS patients, transplantation during the early stages of disease is detrimental, and that improved outcomes are attained by delaying transplantation until disease progression.
   D. All of the above.

9. **Which of the following ethnic variations in disease behavior and progression have been observed in MDS patients?**
   A. MDS occurs at a younger age in Japanese and Chinese patients than in Western patients.
   B. Compared to Western patients, Japanese patients tend to have more cytopenias but better prognosis and lower risk of leukemia, and Chinese patients have a lower incidence of chromosome 5 and 7 abnormalities.
   C. White American, African-American, and Irish patients have significantly higher rates of acute GVHD and treatment-related mortality than do Japanese patients.
   D. All of the above.

10. **Which of the following is true regarding cultural, environmental, and psychosocial barriers to transplantation?**
    A. In the best treatment centers, only approximately one fourth of eligible patients with an available HLA-identical donor actually receive this treatment.
    B. In the United States, outreach efforts have made participation in clinical research trials, which offer the best outcomes, available to large numbers of patients in medically underserved areas.
    C. Comorbidity and socioeconomic status are the demonstrated causes of worse outcomes from allogeneic transplantation in Hispanic than white patients treated in the United States.
    D. All of the above.

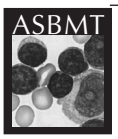
CME Assessment Test Answer Sheet

Release Date: June 30, 2006 **Last Review Date: June 30, 2006** **Expiration Date: June 30, 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 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					



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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.

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

I have read these articles on the Treatment Strategies for Myelodysplastic Syndromes, 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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