Blood and Marrow TRANSPLANTATION

REVIEWS

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IN THIS ISSUE

Myelodysplastic Syndromes: Rejuvenating the Senescent

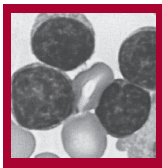
John R. Wingard, MD, Editor

The myelodysplastic syndromes (MDS) have often been called the poster child for apoptosis gone awry: in some cases death (to hematopoietic progenitors) comes too infrequently, in other cases it comes too readily. The quest to better understand its basis and to translate this understanding into therapeutics is only beginning, but already several therapies have emerged and others are in development.

For now, there is only one curative therapy for MDS: hematopoietic cell transplantation (HCT). Indeed, it can be argued that the pivotal clinical decision for each patient with MDS is whether HCT should be offered and if so when. Critical elements of the decision include the prognosis and impact of the MDS manifestations facing the patient, the fitness of the patient for HCT, and whether a suitable donor is available. The tempo of the disease process also influences the timing of the transplantation option. For those in whom HCT is not appropriate, supportive care and an increasing array of treatment options to influence apoptosis are the choices to be considered.

Developments in new and emerging therapies, both transplantation and nontransplantation, are the subject of a satellite symposium presented at the 2007 BMT Tandem Meetings in Keystone, Colorado. In the first presentation, Dr. Richard Stone discusses the general approach one should take in making clinical decisions in patients with MDS and discusses the various approaches for different types of MDS. Dr. Joachim Deeg discusses the factors that should be weighed in choosing when to offer transplantation and discusses the expectations one can reasonably anticipate. Dr. Douglas Smith presents some innovative options being explored to improve transplantation outcomes in high-risk disease.

It truly appears that emerging therapies are finally giving new life to an old problem that resisted efforts for decades. These efforts now offer the prospect of improving quality of life for some, extending survival for others, and for some cure.



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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.

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10 Young Clinicians and Investigators Selected for ASBMT Training Course

Ten new clinicians and investigators have been selected to participate in the first ASBMT Transplant Clinical Research Training Course, in mid-July in Keystone, Colo.

The six-day course is designed to assist fellows and young faculty in career paths toward successful clinical research in blood and marrow transplantation. The participants were selected competitively from among 30 submitted applications, each including a proposed research project.

Major funding for the clinical research training course is being provided by **Amgen, Merck, PDL BioPharma, Genzyme Transplant and Abbott Molecular.**

The fellow-in-training participants will be:

- Ann Mullally, MD, Massachusetts General Hospital, Boston
- Phillippe Armand, MD, PhD, Dana-Farber, Boston
- Carlos Almeida Ramos, MD, M.D. Anderson, Houston
- Alana Kennedy-Nasser, MD, Baylor, Houston
- Kirsten Williams, MD, National Cancer Institute, Bethesda
- Jeanne Palmer, MD, Duke, Durham
- Guillermo J. Ruiz Delgado, MD, Hospital Universitario, Monterrey, Mexico

The junior faculty participants will be:

- Guenther Koehne, MD, PhD, Memorial Sloan-Kettering, New York
- Carrie Kitko, MD, University of Michigan, Ann Arbor
- G. Doug Myers, MD, Baylor, Houston

The course directors are Daniel Weisdorf, MD, of the University of Minnesota, and Nelson Chao, MD, of Duke University. They, together with six other faculty members, will lead the sessions, as well as share their career stories and counsel. Free time for rest, recreation and creative thinking is built into the schedule.

The concept of a clinical research training course emanated from an ASBMT Board of Directors strategic planning retreat. "The board members felt that existing fellowship programs don't adequately train clinical fellows in the principles of clinical research in blood and marrow transplantation," said Armand Keating, MD, past-president and chair of the committee to develop the training course.

"Training programs typically don't fully cover the principles of taking basic research findings from the laboratory to the clinic, nor do they adequately prepare the best young physicians for academic careers in blood and marrow transplantation. We expect the training course to address those deficiencies and help close the gap," he said. The faculty members for the transplant clinical research training course are:

- Chris Bredeson, MD, MSc, Medical College of Wisconsin – clinical trial development, monitoring and data management
- Dr. Chao – mechanisms of GVHD, graft manipulation, animal models and grant writing/grantsmanship
- Corey Cutler, MD, MPH, Dana-Farber Cancer Institute – GVHD, new drug studies and translational studies
- Armand Keating, MD, Princess Margaret Hospital Cancer Center, Toronto – stem cell biology, gene therapy and translational studies
- Ginna Laport, MD, Stanford University – cancer trials, new agents and multicenter trials
- Stephanie Lee, MD, MPH, Fred Hutchinson Cancer Research Center – quality of life/late effects
- Brent Logan, PhD, Center for International Blood and Marrow Transplant Research – statistics
- Jeffrey Miller, MD, University of Minnesota – cellular and molecular mechanisms of immunologic anti-cancer therapy
- Dr. Weisdorf – GVHD clinical and translational trials and complications of transplant

Web Site Helps BMT Personnel Respond to Radiation Incidents

A Web site for helping BMT physicians respond to radiation incidents has been created by the Radiation Injury Treatment Network (RITN), a joint project of the ASBMT and the National Marrow Donor Program.

The Web site provides guidelines and protocols for comprehensive evaluation and treatment of victims of radiation exposure or other marrow-toxic injuries. The information is based on more than 20 years of the U.S. Navy's leadership in contingency preparedness through the NMDP and was prepared by representatives of transplant centers, donor centers and cord blood banks. The groups have been meeting since 2003 to prepare for radiological or chemical events that result in hematopoietic toxicity.

The Web site address is *www.nmdp.org/RITN*.

Designed for expansion and update in the coming months, the Web site complements the Radiation Event Medical Management (REMM) Web site at *remm.nlm.gov* that was introduced in March by the U.S. Department of Health and Human Services. Whereas the REMM site has a broad focus on first-responder triage and community and hospital-wide incident response, the RITN site is specific to hematopoietic cell therapy.

FACT Introduces New Web Site

The Foundation for the Accreditation of Cellular Therapy has updated its Web site.

The Web site has the same address, *www.factwebsite.org*, but has been rearranged, expanded and made faster and easier to navigate.

Visitors can search for accredited BMT facilities and cord blood banks, learn about accreditation requirements, locate and sign up for workshops, find out how to become an inspector and contact the FACT leadership and staff.

ASBMT

Symposium Report

Blood and Marrow TRANSPLANTATION REVIEWS

Managing the Myelodysplastic Syndrome Patient Through Transplantation

Adapted from the CME symposium "*Managing the MDS Patient Through Transplantation*," held on February 8, 2007, at the BMT Tandem Meetings in Keystone, Colorado. This activity is sponsored by the Medical College of Wisconsin and an educational grant from Pharmion Corporation.

MEDICAL COLLEGE OF WISCONSIN CME program

Faculty

B. Douglas Smith, MD
The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University
Baltimore, Maryland

Richard M. Stone, MD
Dana-Farber Cancer Institute
Boston, Massachusetts

H. Joachim Deeg, MD
Fred Hutchinson Cancer Research Center
Seattle, Washington

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 individual educational activity has disclosed all relevant financial relationships. The presenting faculty members have all made the proper disclosures, and the following relationships are relevant:

B. Douglas Smith, MD, has received honoraria from Pharmion and has been a speaker for Pharmion.

Richard M. Stone, MD, has received honoraria from Pharmion and Celgene. He also has been a speaker for Pharmion and Celgene.

H. Joachim Deeg, MD, has received honoraria from Pharmion and Celgene. He also has been a speaker for Pharmion and Celgene, and he has received grant support for research from Genzyme and PDL BioPharma.

Needs Assessment

The myelodysplastic syndromes (MDS) are a relatively rare disease. Estimates are that 15,000 patients in the US have MDS, but that many more patients may be undiagnosed. Often BMT physicians may help with the diagnosis of these patients, and therefore, there was a need for education on the disease characteristics and available treatment options.

Target Audience

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

Learning Objectives

- Define key disease characteristics including the epidemiology, pathophysiology, and classification of the myelodysplastic syndromes.
- Discuss the role of epigenetics including DNA hypermethylation and gene silencing in MDS.
- Compare the new treatment options in MDS.

Accreditation Statement

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

Continuing Medical Education Credit

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

Myelodysplastic Syndromes: Nontransplantation Options and Algorithms

Richard M. Stone, MD

Introduction

Myelodysplastic syndromes (MDS) represent a group of clonal bone marrow stem cell disorders typically characterized by hypercellular marrows, peripheral cytopenias, and cell functional abnormalities that result in part from a failure of hematopoietic differentiation. This group of diseases is highly heterogeneous with variable natural histories. Patient death generally occurs because of bone marrow failure—with or without conversion to AML. The only curative modality is allogeneic bone marrow transplantation.

Another aspect of disease heterogeneity is the lack of a clear-cut unifying pathophysiology. MDS subtypes without excess blasts may be due to overactive apoptosis, accounting for a cellular bone marrow concurrent with low peripheral blood counts. Other features could include inhibitory cytokines, such as believed to be the case in aplastic anemia, accounting for excessive autoimmunity. With more aggressive excess blast subtypes of MDS, similar pathophysiological issues to those associated with any neoplasm must be considered: too little apoptosis, too much proliferation, and a failure to differentiate. Except for certain rare subtypes of MDS involving an activation of the tyrosine kinase (PDGFR-β) observed in a few patients with chronic myelomonocytic leukemia, we are far from a complete understanding of the genetics of this condition.

MDS Overview

One essential question physicians and patients ask after a diagnosis of MDS is, "What is the prognosis of the patient's disease?" Relevant data include accurate information regarding the histological features of the disease based on subclassification according to the WHO or French-American-British classification systems [1]. Most clinicians employ the International Prognostic Scoring System [2], which requires knowledge of how many blasts are present in the marrow, a cytogenetic analysis, and blood counts.

As always in the practice of medicine, licensed professionals must "get to know the patient," thoroughly reviewing his or her symptoms and complete medical history to achieve the goal of appropriate treatment. Critical issues in addition to the International Prognostic Scoring System score include patient age, performance status, and comorbid diseases.

A vast array of potential therapies might be applied in patients with MDS (Table 1). There are several FDA-approved drugs and many other treatments remain under investigation. Some of the available therapies and those in development may apply more appropriately to indolent histologies versus aggressive histologies. Moreover, not every MDS patient necessarily requires immediate treatment.

Treatment Options: Supportive Care and Immunosuppression

When a stem cell transplantation is ruled out for the short- or long-term because of prognosis, age, or comorbid conditions, one must look at what types of nontransplantation therapies are now available. Almost every patient with MDS will receive supportive care, which means ongoing therapies to maintain blood counts without dealing with the primary pathophysiology. For example, almost every patient with MDS is exposed to erythropoietin or darbopoietin. The optimal dosage and schedule of these 2 drugs remain controversial. The value of adding G-CSF to erythropoietin requires further study [3].

A patient with MDS may often receive many transfusions with resulting iron overload, possibly leading to cardiac, hepatic, and pancreatic dysfunction. A new iron-chelating drug, deferasirox, is now available. It is administered orally, as compared to a previously available iron chelator, deferoxamine, which required subcutaneous administration and was generally poorly accepted by patients. Whether the relatively few good-prognosis yet heavily transfused MDS patients who could develop complications because of iron overload should be aggressively treated with iron chelation, such as has been done successfully in thalassemia, remains controversial.

The myeloid growth factors GM-CSF and G-CSF routinely increase the white blood counts; however, they do not appear to make a difference in the natural history of MDS. Platelet transfusions should be administered judiciously. Whether AMG 531, a thrombopoietic agent shown to be effective in immune thrombocytopenic purpura, will be useful in MDS, remains to be determined [4].

Immunosuppressive therapy can be considered for those with indolent histologies in which inhibitory cytokines and autoimmunity may be playing significant roles. Such treatments would address any potential overlap of MDS and aplastic anemia. Young and colleagues at the National Cancer Institute [5] have reported that antithymocyte globulin can be a very effective therapy for a subset of patients with MDS, particularly those who are younger, who have a low platelet count, and who have an HLADR-15 HLA type.

Table 1. Current and Potential Treatment Options

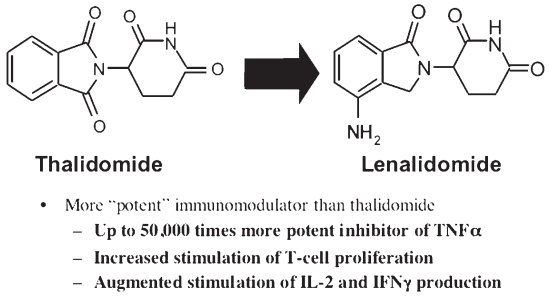
For Lower Risk	For Higher Risk
Erythropoietin (EPO)	Angiogenesis inhibitors
EPO + G-CSF	Epigenetic therapy
Immunomodulating agents	DNA methyltransferase inhibitors
Thalidomide	HDAC inhibitors
Lenalidomide	Enhance autoimmunity
Arsenic trioxide	Signal transduction inhibition
Amifostine	Farnesyltransferase inhibitors
Antithymocyte globulin	Tyrosine kinase inhibitors
Enhance autoimmunity	GST inhibitors
Epigenetic therapy	High-dose nontransplantation
Azacitidine	options
Decitabine	Chemotherapy
	High-dose chemotherapy with
	AHSC rescue
Angiogenesis inhibitors	Stem cell transplantation options
	Standard
	Reduced intensity

Treatment Options: Immunomodulation with Lenalidomide

For MDS patients exhibiting indolent histologies, one important consideration is lenalidomide, recently approved by the FDA. Based on its presumed antiapoptotic and antiangiogenic properties, Raza et al [6] have studied using thalidomide in some indolent-histology MDS cases with occasional responses noted, albeit with significant side effects.

Lenalidomide is a potent immunomodulating drug that is non-neurotoxic, relatively nonteratogenic, and also nonsedating, which are advantages compared with the structurally related thalidomide (Figure 1). List et al [7] conducted a Phase I trial in which lenalidomide was given to MDS patients and showed that patients with a 5q- cytogenic abnormality exhibited impressive responses. Based on these results, two Phase II studies were simultaneously conducted to provide additional information about potential uses of lenalidomide in treating MDS.

One such study was restricted to patients with 5q- cytogenic abnormality alone, or associated with other abnormalities. The other study was restricted to patients that did not



Lenalidomide: pharmacologic evolution. This figure was published in Seminars in Oncology, Volume 28, Stirling D, Thalidomide: a novel template for anticancer drugs, 602-606, Copyright Elsevier, 2001.

have a 5q- cytogenetic abnormality. For both studies, patients needed to have a neutrophil count greater than 500, a platelet count greater than 50,000, the presence of de novo MDS, and low- or intermediate-risk MDS.

Both the 5q- patients and the non-5q- patients were heavily transfusion-dependent, with median red cell requirements of 4 to 5 units in the 8 weeks prior to study entry. In patients with 5q-, approximately three fourths had 5q- as an isolated abnormality, while only one third had 5q- syndrome [6-8].

The Phase II trial results confirmed the outstanding results in 5q- patients who had a 66% rate of transfusion independence [7,8]. The duration of the response was at least 47 weeks and a 5.4 g/dL median rise in hemoglobin was noted. The time to response was 5 weeks. Lenalidomide was somewhat successful in treating patients with non-5q- MDS who had a 25% chance of becoming independent of transfusions [6-8]. In patients with isolated 5q-, about 50% had resolution of chromosomal abnormalities. This result suggests potential disease-modifying activity in treating the 5q- subtype of MDS [6-8].

The mechanism of action of lenalidomide is still unclear. Although it is a fairly well-tolerated drug, lenalidomide does cause cytopenia, which warrants monitoring of the platelet count and the neutrophil count [6-8].

Treatment Options: The DNA Methylation Agents Azacitidine and Decitabine

The goal of so-called "differentiation therapy" is to overcome the presumed pathophysiological block in hematopoietic maturation. Promotion of differentiation requires eliciting transcription of silenced genes (Table 2). Hypomethylation of DNA is one approach. The second is to acetylate the histone protein coat around the DNA, which allows transcription. A very important study conducted by the CALGB compared the DNA hypomethylating agent azacitidine to supportive care in MDS [9,10]. The study included an early crossover as well as an associated quality-of-life analysis. The reported results documented a complete remission rate of 7%, a partial remission rate of 16%, and a hematologic improvement rate of 36% in patients randomized to azacitidine. In patients randomized to supportive care but crossed over, response to azacitidine was still possible [9,10].

Decitabine, another DNA hypomethylating agent, was studied by Wijermans and colleagues in Belgium [11] and was eventually translated into a Phase III trial of decitabine versus observation, the results of which were similar to the azacitidine trial [12]. The study used an intravenous formulation of decitabine that was given every 8 hours for 3 consecutive days. In the high-risk group of patients, a delay in time to transformation to AML or death was observed compared to supportive care.

Based largely on the M.D. Anderson Cancer Center trial led by Kantarjian and colleagues, there has been interest in novel dose schedules of decitabine [13]. The most useful schedule was 5 days of decitabine of 20 mg/m^2 given intravenously daily every 4 weeks. This data requires confirmation from larger trials in multiple institutions.

Ongoing Research and Possible Future Treatment Options

In addition to the 3 available therapies discussed, several other novel therapies are being developed. Farnesyltransferase inhibitors, which may work by preventing normal function of the RAS proto-oncogene, but probably with alternative mechanisms, have been associated with a 30% response rate [14]. Two intergroup trials in MDS are ongoing, including one for low-risk patients combining erythropoeitin plus lenalidomide based on preclinical data that erythropoietic agents might potentiate the effect of lenalidomide on reducing transfusions. The other intergroup trial is a large phase II trial being conducted for high-risk patients that combines the DNA hypomethylating agent, azacitidine, with a histone deacetylase inhibitor, MS-275. The preliminary data reported at ASH in December 2006 were positive [15].

Raza and colleagues have conducted preliminary research with a GST analog that modifies c-jun activity, which seems to be able to promote synthesis of red blood cells [16]. Other strategies include MAP kinase inhibition in low-risk disease [17], and PTK 787, a VEGF receptor tyrosine kinase inhibitor, that is being investigated by the CALGB [18].

Conclusion

In conclusion, the general algorithm for MDS is to consider allogeneic stem cell transplantation, particularly in high-risk patients under the age of 55 (Table 3). If patients require transplantation, but are between the ages of 55 to 70, a nonmyeloablative

Table 2. Epigenetic DNA Modifications

Epigenetic gene silencing	Therapeutic strategies
DNA Hypermethylation	DNA methyltransferase inhibitors (eg, azacitidine, decitabine) promotehypomethylation of DNA, allowing expression of previously silenced genes
Chromatin remodeling	Histone deacetylase inhibitors (eg, valproic acid, phenylbutyrate) restore chromatin structure and gene transcription
Histone deacetylation alters structures of DNA during gene transcription	

Table 3. General Algorithm

Consider allogeneic stem cell transplantation
If poor prognosis and under 55 years of age: stnd MUD or sib
If poor prognosis and 55 to 70 years of age: nonmyeloablative transplantation
Cytoreduction pre-alloHSCT (ind'n versus azacitidine/decitabine)
Trial of EPO in selected patients (EPO < 500 mIU/μL); add low dose G-CSF
Lenalidomide in 5q- patients
Clinical trial, if possible, if not, consider:
ATG in hypoplastic
Lenalidomide in RA or RARS
Azacitidine or decitabine in all cases

transplantation should be discussed. For most 5q- patients, lenalidomide would be recommended, because of the high response rate both clinically and cytogenetically. For other patients, a DNA hypomethylating agent, such as azacitidine or decitabine, can be considered in both low-risk and high-risk disease. However, all nontransplantation candidates, with the possible exception of those with 5q- cytogenetic abnormalities, should be strongly considered for enrollment in a clinical trial.

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Optimization of Transplantation Regimens for Patients with Myelodysplastic Syndromes

H. Joachim Deeg, MD

Myelodysplastic syndromes (MDS) are classified according to several systems; the WHO classification, which uses predominantly the marrow myeloblast count and the number of cell lineages involved, is currently recommended. This approach has broken down the groups into distinct prognostic subgroups (Table 1). The International Prognostic Scoring System (IPSS) incorporates peripheral blood cell counts and chromosomal abnormalities, and recent data suggest that transfusion dependence should also be considered [1]. If a patient is categorized in the lowest risk group and does not require transfusions, life expectancy may be in the range of a decade. In the highest risk group (eg, with high myeloblast counts, high-risk cytogenetics, and transfusion dependence), life expectancy may be only a few months. Patients in these high-risk groups should be considered for more aggressive treatment as the first choice of therapy [2-4] (Table 2). The many questions for discussion between doctors and patients when considering stem cell transplantation include: Should a patient with a high blast count receive induction chemotherapy? (A definitive answer to this question is not available.) What source of stem cells should be used? How does a patient's age affect treatment decisions? Considering a patient's age, what should the conditioning intensity be? What is the impact of comorbid conditions, a variable that is strongly correlated with age? And finally, how can new treatment modalities be incorporated into the transplantation approach? (Table 3).

Table 1. Current Classifications of Myelodysplastic Syndromes

Myeloblasts/number of cell lines involved	WHO
Blood cell counts/chromosome abnormalities	IPSS
Transfusion requirements	WPSS

Disease Stage and Transplantation Outcome

As already stated above, based on the IPSS risk-categorization data [3], the median life expectancy with MDS may range from more than a decade to less than half a year. A decision analysis by Cutler et al [5] showed that patients in the highest IPSS risk categories (scores >1.0) had the best life expectancy if they received transplants (from HLA identical donors) without much delay, whereas patients with lower risk scores might benefit from initial conservative management.

Table 2. Myelodysplastic Syndromes Evolution

Transformation into leukemia
Progressive decline in blood cell counts

Table 3. Questions When Approaching Transplantation

Importance of disease stage for timing and outcome?
Is there a role for induction chemotherapy?
Which source of stem cells?
Does patient age affect the strategy?
What conditioning intensity?
What is the impact of comorbid conditions?
How will new treatment modalities affect the transplantation?

Data published a few years ago by researchers from the Fred Hutchinson Cancer Research Center (FHCRC) in Seattle, WA [6], used the IPSS categorization to determine how the pretransplantation IPSS score would impact on posttransplantation outcomes (Figure 1). Patients with low scores had significantly higher probabilities of survival than patients with high scores, predominantly because of a higher incidence of MDS relapse in the higher risk patients. The 3 big hurdles in transplantation remain relapse, nonrelapse mortality, and graft-versus-host disease with associated infections.

Is pretransplantation induction chemotherapy useful in preventing posttransplantation relapse? The final answer is not yet available. A study by the M.D. Anderson group as reported by de Lima et al [7] indicated patients in remission following chemotherapy had a higher probability of long-term survival than patients who did not achieve remissions. Data from a smaller retrospective study completed at the FHCRC [8] did not support those conclusions.

The current trend in the transplantation community is in favor of using peripheral blood as the source of stem cells for MDS-related transplantation, although there are pros and cons for this approach. Advantages of the use of peripheral blood cells include reduced early mortality and lower incidence of relapse in high-risk patients. [9] (Table 4). Chronic graft-versus-host disease tends to be more common than with marrow, although this may not have a significant impact on long-term survival. While the results of randomized trials support the use of peripheral blood in patients who receive transplants from HLA identical siblings [10], the answer is less clear for unrelated donor transplants; we are awaiting the outcome of a currently ongoing randomized trial.

Table 4. Granulocyte Colony-Stimulating Factor Mobilized Peripheral Blood Progenitor Cells

Reduced early mortality
Lower incidence of relapse
But: more chronic graft-versus-host disease
Use only with advanced disease?

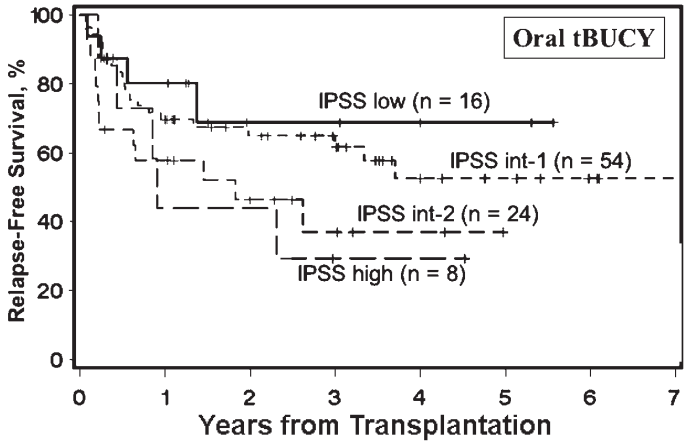

Figure 1. Relapse-free survival for patients 6 to 66 years old, with related or unrelated donors. This research was originally published in Blood. Deeg HJ, Storer B, Slattery JT, et al. Conditioning with targeted busulfan and cyclophosphamide for hematopoietic stem cell transplantation from related and unrelated donors in patients with myelodysplastic syndrome. *Blood*. 2002;100:1201-1207. © the American Society of Hematology.

Comorbid Conditions and Conditioning Intensity

With regard to comorbid conditions, the central issue is nonrelapse mortality. The use of reduced-intensity conditioning regimens may indeed reduce toxicity and early mortality, but there is strong evidence that the incidence of relapse is higher.

With decreased conditioning intensity, transplantation success will increasingly depend on the immune effects mediated by donor-derived cells (Figure 2).

In recent studies conducted at FHCRC [8], overall survival with nonmyeloablative regimens (ie, low-dose total body irradiation + fludarabine) was compared to survival with ablative regimens (busulfan + cyclophosphamide). Differences in outcome were not significant, but patients in the 2 cohorts differed in several respects.

A large retrospective study reported in 2006 by Martino et al [11] also found that overall survival and relapse-free survival did not significantly differ among the groups receiving high-dose regimens versus those receiving reduced-intensity conditioning. Based on our current knowledge, factors that best determine a beneficial outcome after transplantation include early

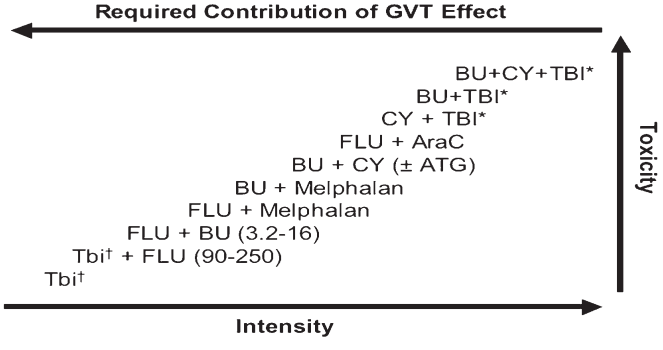

Figure 2. Conditioning regimens. GVT indicates graft-versus-tumor. *Total body irradiation (TBI) ≥12 Gy. †2 cGy.

Table 5. Factors that Determine Outcome after Transplantation

Disease stage
Pretransplantation chemotherapy (?)
Comorbid conditions
"Intensity" of transplantation regimen
Pretransplantation (Flu, TBI, etc)
Posttransplantation (MMF)
Source of stem cells

stages of MDS, low comorbidity score, and the intensity of the transplantation regimen. There is some evidence that changes in the immunosuppressive regimen given after transplantation may modify long-term results. Other factors include, as discussed already, the source of stem cells, and possibly the use of pretransplantation chemotherapy (Table 5). Controlled prospective studies are needed.

Who, When, and How?

Transplantation using "conventional" conditioning regimens might be the best strategy for younger patients. Patients up to 65 years of age (with an HLA-identical sibling donor) and up to 60 years of age (with an unrelated donor) are currently candidates for "conventional " transplantation. Reduced intensity regimens are recommended for those patients who have comorbid conditions, and possibly patients who have received successful pretransplantation induction therapy. Patients who have a very high transfusion requirements should probably be considered for transplantation earlier in the disease course than suggested by their IPSS staging. When treating patients with less advanced MDS, physicians might want to observe initially and treat conservatively. The availability of new drugs for palliative treatment of MDS may offer new treatment strategies.

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Myelodysplastic Syndromes: Posttransplantation Strategies to Improve Outcomes

B. Douglas Smith, MD

Allogeneic stem cell transplantations (alloSCT) offer the potential to cure patients with myelodysplastic syndromes (MDS). Unfortunately, most patients will not be candidates because of their age, lack of a suitable donor, or their poor medical condition. Still others will go through the procedure and still relapse from their underlying disease. Efforts have focused on improving the outcomes with alloSCT for patients with MDS and recent reports suggest that there may be ways to modify the posttransplantation setting to minimize the relapse that is expected in patients with high-risk disease.

There are many factors that a physician must take under consideration when planning an alloSCT (Table 1). These factors also play critical roles when developing strategies that alter the transplantation to improve results. One such variable is a high disease burden at the time of transplantation, which is associated with an increased risk of posttransplantation relapse. A second variable is the donor serving as the source of the stem cells. Determining the graft-versus-host prophylaxis and the preparative regimen for the alloSCT round out these important factors.

Table 1. Stem Cell Transplantation for Myelodysplastic Syndrome: Questions in Need of Answers

Type of stem cell transplantation?
Source of stem cells
Myeloablative versus nonmyeloablative preparation
Graft-versus-host disease prophylaxis
Best candidates for bone marrow transplantation?
Age cutoff?
Low-risk patients = do better with transplantation
High-risk patients = need transplantation
Induction chemotherapy in high-risk patients?
Three agents recently approved for myelodysplastic syndrome

Researchers at Johns Hopkins have long favored the use of intensive, myeloablative preparative regimens followed by T-cell–depleted allografts for patients undergoing alloSCT for MDS. A recent review of outcomes in a small group of 31 patients, (median age, 46 years; range, 29-65 years), who underwent a matched sibling donor transplantation using a myeloablative preparative regimen and T-cell depletion, supported other reports that long-term survival for high-risk patients was poor [1]. However, it was noted that the alloSCT was well tolerated, even by the older patients in the group.

This group then went on to develop a follow-up protocol designed to decrease relapse following a similar alloSCT by added systemic

Table 2. Options for Post–Stem Cell Transplantation Modifications

Early donor lymphocyte infusions
Immunotherapy–vaccine approaches
Granulocyte-macrophage colony-stimulating factor–secreting leukemia cell vaccines
Maintenance strategies
Azacitidine

- Day -12 to day -9: Fludara 30 mg/m² + AraC 2 g/m² + AMSA 100 mg/m²
- Day -8 to day -5: Rest
- Day -4: TBI 4 Gy
- Day -3 and -2: CY 40 (60) mg/kg + ATG 10 (20) mg/kg
- Day -1: ATG 10 (20) mg/kg

- Day 0: PBSCT
- GVHD prophylaxis: CSA + MMF

- Day +90 DC Immunosuppression
- Day + 120 DLT in escalating doses
- Day + 150 "
- Day + 180 "

Figure 1. Reduced-intensity conditioning FLAMSA for high-risk acute myeloid leukemia/myelodysplastic syndrome.

growth factors in the post-SCT setting. This protocol evolved from laboratory work suggesting that growth factors resulted in enhanced differentiation in leukemia and MDS cell lines. These data have been recently reviewed, and senior clinical fellow Dr. Erica Warlick has submitted a manuscript reporting them for publication [1]. Her report of 52 patients once again determined that a fully ablative alloSCT using a T-cell–depleted allograft was well tolerated in a particularly poor risk and older group of MDS patients (median age, 56 years). She noted that patients who underwent alloSCT in remission and those with low IPSS risk had the best outcome. However, the addition of the post-SCT growth factors may have offered some benefit in the high IPSS group, noting an improved survival rate to 20% at 3 years compared to previous transplantations in MDS patients without post-SCT growth factors. The protocol did not increase the risk of graft-versus-host disease, nor did it increase the risk of graft failure.

Recently, early results from treatment approaches trying to improve alloSCT outcomes for MDS patients were presented at the December 2006 annual meeting of the American Society of Hematology (Table 2). One abstract [2] focused upon early intervention with donor lymphocytes; the second abstract [3] concentrated on immuno-based therapy with a vaccine approach; and the third abstract [4] considered a maintenance strategy using azacitidine following alloSCT.

Early Intervention with Donor Lymphocytes

The German Cooperative Group study presented by Kolb [2] examined many aspects of MDS transplantations, including the factor of the preemptive donor lymphocytes. One challenge in developing a treatment strategy is that elderly patients are often not ideal candidates for transplantation. Several important factors were gleaned from previous cooperative studies: the use of chemotherapy for patients with treatment-related leukemia or treatment-related MDS often failed to produce durable remissions, preparative regimen toxicity was associated with increased cytokines and inflammation that were in turn associated with high rates of graft-versus-host disease, and patients with de novo acute myeloid leukemia did best if in complete remission at the time of transplantation.

The German study postulated that reduced-intensity transplantation approaches might be incorporated with effective anti-leukemia therapy given prior to alloSCT in patients with active disease and given following the transplantation in the form of scheduled donor lymphocytes. This study group incorporated fludarabine, ara-C and amsacrine as the initial antileukemia basis for treatment (Figure 1). The transplantation consisted of TBI or busulfan, cytoxan and ATG, cyclosporin and MMF for graft-versus-host disease prophylaxis, and scheduled DLI in patients without graft-versus-host disease by day 90. The DLI planned escalating doses starting at approximately day 120 and included 1×10^6/kg, then 5×10^6/kg, and finally 1×10^7/kg on days 120, 150, and 180, respectively (Figure 2).

Table 3. Allogeneic Stem Cell Transplantation for Myelodysplastic Syndrome and sAML Following Reduced-Intensity Conditioning and Preemptive Donor Lymphocyte Transfusion: Conclusions

AlloSCT offers long-term complete remission in sAML + MDS
Toxicity = the major problem:
- Younger versus older patients
- Busulfan to TBI in conditioning preparation
- Reduced-intensity conditioning permits the treatment of elderly patients

Preemptive DLT may decrease relapse

- RIC Prep, age > 60 years = FLAMSA + BUS (8mg/kg)
- RIC Prep, others = TBI x 4 Gy
- DLI = 3 dose escalations planned (if no infection or GVHD):
  - Day 120 = 1 x 10^6/kg
  - Day 150 = 5 x 10^6/kg
  - Day 180 = 1 x 10^7/kg

sAML	Overall	F + BUS	F + TBI
Survival at 2 years	64%	70%	61%
Non-relapse mortality at 2 yrs		9%	37%
Relapse or progression rate	25%		

Figure 2. Allogeneic stem cell transplantation for myelodysplastic syndrome and sAML following reduced-intensity conditioning and preemptive donor lymphocyte transfusion.

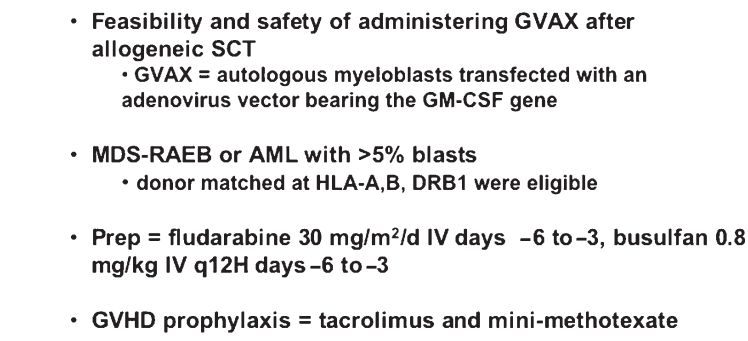

Figure 3. Granulocyte-macrophage colony-stimulating factor–secreting leukemia cell vaccinations after allogeneic reduced-intensity peripheral blood stem cell transplantation for advanced myelodysplastic syndrome or refractory acute myeloid leukemia.

Their report showed the best survival of 70% at 2 years post-alloSCT in the group receiving fludarabine and busulfan preparative regimen with a nonrelapse mortality of less than 10% (Table 3). Overall, their approach was well tolerated and it appeared to reduce the number of expected early relapses. Developing a strategy to improve the antitumor effects of alloSCT incorporating pre-SCT chemotherapy and post-SCT DLI may improve long-term outcomes and make transplantations more successful for high-risk patients.

What about Immunotherapy?

Dr. Ho and his colleagues at the Dana-Farber Cancer Institute [3] have proposed to develop individual tumor vaccines for subjects with active disease at the time of transplantation. The goal was to use the individual vaccines to stimulate an antitumor effect following the transplantation. The trial proposed was to determine feasibility of creating individual patient tumor-based vaccines by transfecting the patient's tumor cells with the granulocyte-macrophage colony-stimulating factor gene (to produce a local, injection site immune-stimulatory effect) using an adenovirus-based approach (Figure 3).

The protocol called for a fludarabine and busulfan preparative regimen and tacrolimus and minimethotrexate for graft-versus-host disease prophylaxis. Initially, 18 patients, with a median age of 63 years, were enrolled. The team was successful in producing a vaccine for all 18 of the subjects enrolled; however, only 9 subjects received vaccine in part due to poor disease control. Of the 9 subjects who remained on the protocol, 6 were alive with stable disease 6 months later with 4 of the 5 who completed all vaccines maintaining disease stability at the time of the report. As expected, those with the highest risk disease showed early progression. The early results from this trial support the feasibility of producing individual tumor vaccines and suggests that this approach merits further study.

Maintenance Therapy with Azacitidine

An abstract by Soriano et al [4] from the M.D. Anderson Cancer Center reported early results on the addition of azacitidine in the post-SCT setting. They reported on a cohort of 12 patients with active disease at the time of transplantation who underwent either a matched-sibling or unrelated-donor transplantation. The preparative regimen included gemtuzumab, fludarabine, and melphalan and antithymocyte globulin was added for patients undergoing the transplantation using an unrelated donor. The M.D. Anderson team proposed studying the addition of azacitidine using several different azacitidine doses and schedules. A continual reassessment model and Bayesian statistics were employed so that physicians could best ascertain how to move patients through treatment protocols based on the toxicity of prescribed regimens. The study reported on 12 patients, median age 55 years, and saw no relapses at a median of 5 months posttransplantation (Figure 4). Although it is still too early to draw meaningful conclusions, having patients in remission following alloSCT when all had active disease prior is noteworthy. Azacitidine did not appear to have any impact on graft-versus-host disease and the donor stem cell engraftment was stable with 100% donor chimerism in all patients. Ultimately, the hope is to use a safe and effective transplantation platform and then build on the platform by the addition of agents with antitumor specificity to ultimately decrease relapse and improve outcomes for MDS patients.

Ways to Improve Outcomes

There are many transplantation-related variables and now novel transplantation approaches that impact the outcomes for patients undergoing alloSCT for MDS. Physicians must make several choices when planning an alloSCT for their patients (Figure

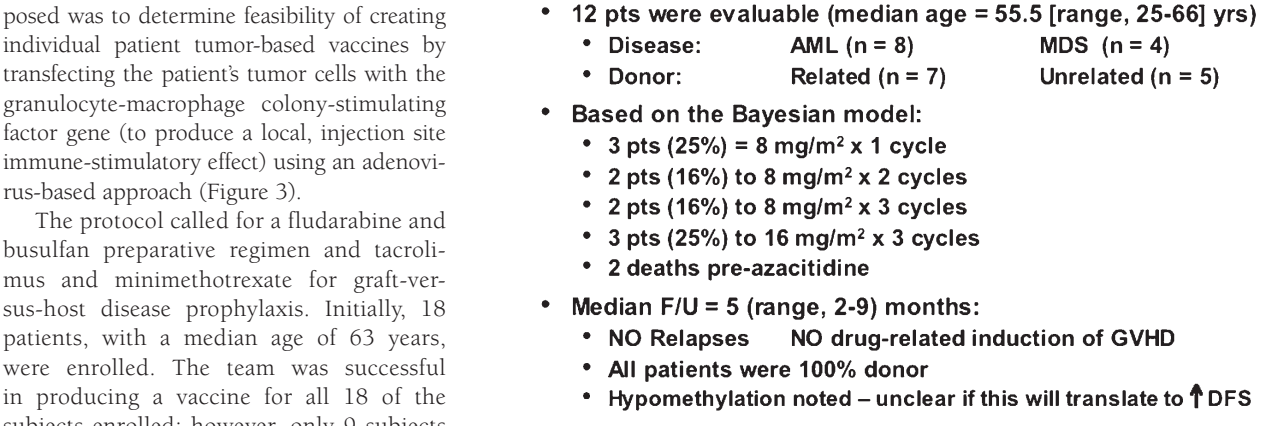

Figure 4. Maintenance therapy with 5-azacitidine after allogeneic stem cell transplantation for acute myelogenous leukemia and high-risk myelodysplastic syndrome: a dose and schedule finding study.

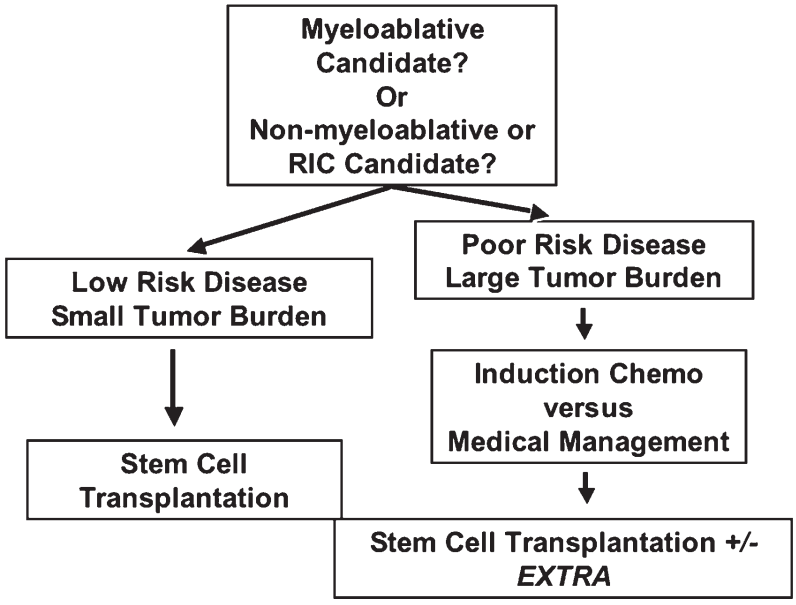

Figure 5. Flow chart for determining treatment candidacy.

5) including whether to offer induction therapy prior to moving to alloSCT, the best source of donor stem cells for their patient, and the best way to deliver the transplant. In particular, patients with active disease at the time of alloSCT and those with high-risk MDS have generally had poor outcomes, even with aggressive alloSCT. Current clinical trials are focusing on ways to incorporate new posttransplantation strategies, including planned DLI, immunomodulatory vaccine-based approaches, and the addition of MDS active drugs following transplantation. By constructing a better treatment plan that takes into account both pretransplantation and posttransplantation approaches, the common goal of better treatments for patients with MDS appears to be moving closer to becoming a reality.

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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.

Cornelissen JJ, van Putten WLJ, Verdonck LF, et al: Results of a HOVON/SAKK donor versus no-donor analysis of myeloablative HLA-identical sibling stem cell transplantation in first remission acute myeloid leukemia in young and middle-aged adults: benefits for whom? Blood. 2007;109:3658-3666.

Myeloablative cytoreductive therapy followed by allogeneic hematopoietic stem cell transplantation (allo-SCT) reduces the risk of relapse in patients with acute myeloid leukemia (AML) in first complete remission. However, because of treatment-related mortality, the true survival benefits of this treatment remain unclear. Comparison of patients with versus without a matched sibling donor can be a useful surrogate for randomization in assessing the benefits of allo-SCT. Data from three cooperative AML treatment trials were analyzed to assess the survival impact of allo-SCT for AML patients in first complete remission.

The analysis included 2,287 patients with AML in first remission enrolled in three consecutive HOVON-SAKK collaborative trials between 1987 and 2004. Of these, 1,032 patients were eligible for allo-SCT: ie, they did not have FAB M3 or t(15;17), were in first complete remission after two cycles of chemotherapy, had received consolidation treatment, and were less than 55 years old. Within this group, 326 patients had an HLA-identical sibling donor and 599 did not. (This information was missing for the remaining 107 patients.) The effects of treatment on disease-free and overall survival were assessed overall and for patients at good, intermediate, and poor risk.

Of patients with an HLA-identical sibling, 82% received allo-SCT from this source. In contrast, 65% of patients without a donor received chemotherapy consolidation. At last follow-up, 48% of patients in the donor group were alive and in continuous complete remission compared to 36% of the no-donor group. Relapse rates were 32% versus 59%, respectively—hazard ratio 0.46, with significant reductions in all three risk groups.

Treatment-related mortality was 21% in the donor group versus 4% in the no-donor group. Nevertheless, the donor group had better disease-free survival: 48% versus 37%. On further analysis, the improvement in disease-free survival was significant for donor-group patients at intermediate or poor risk and for those less than 40 years old. In a meta-analysis combining the new data with previous trial reports, the availability of a donor was associated with a 12% improvement in overall survival among AML patients in first complete remission without a favorable risk profile.

The results support the survival benefits of myeloablative conditioning followed by HLA-matched sibling allo-SCT for young-adult patients with intermediate- or poor-risk AML in first complete remission. For patients meeting these criteria, early evaluation of potential sibling donors and subsequent allo-SCT is strongly recommended.

Sun JY, Dagis A, Gaidulis L, et al: Detrimental effect of natural killer cell alloreactivity in T-replete hematopoietic cell transplantation (HCT) for leukemia patients. Biol Blood Marrow Transpl. 2007;13:197-205.

Questions remain as to the impact of natural killer (NK) cell alloreactivity associated with inhibitory ligands of killer immunoglobulin-like receptors (iKIRLs) on the response to hematopoietic cell transplantation (HCT). Although some studies suggest benefits of NK alloreactivity, others report deleterious effects. The association between iKIRLs and the outcomes of T-replete HCT was analyzed.

The retrospective analysis included 378 patients undergoing primary allogeneic transplantation with T-replete grafts at a single center between 1996 and 2003. The diagnosis was acute lymphoblastic leukemia in 101 patients, acute myeloid leukemia and myelodysplastic syndrome in 149, and chronic myeloid leukemia in 128. Based on HLA compatibility, the patients were divided into three groups: HLA class I matched at the antigen level, 260 patients (group 1); HLA class I mismatched at the antigen level, 57 patients (group 2); and mismatched for HLA class I and iKIRLs, 61 patients (group 3). The outcomes of these three groups were compared to differentiate between the effects of HLA and iKIRL mismatches.

Overall survival was 59% in group 1, 49% in group 2, and 30% in group 3. For group 3 patients, overall and event-free survival were significantly lower than in group 2. The reduction in survival for group 3 patients was largely related to their increased risk of relapse. Analysis of HLA-matched transplants in patients lacking iKIRLs also suggested harmful effects of NK alloreactivity. One-year overall survival for patients without the HLA-Cw group 1 or 2 iKIRL was 55%, compared to 67% for those with the iKIRLs.

The results strongly support the theory that NK cell alloreactivity has deleterious effects on the outcomes of T-replete HCT. Posttransplant survival is significantly lower for patients with iKIRL mismatches or without iKIRLs. The authors are conducting a further study to assess the effects of KIR genotype on the outcomes of HCT.

Hockenbery DM, Cruickshank S, Rodell TC, et al, for the orBecGVHD Study Group: A randomized, placebo-controlled trial of oral beclomethasone dipropionate as a prednisone-sparing therapy for gastrointestinal graft-versus-host disease. Blood First Edition Paper, prepublished online January 23, 2007; DOI 10.1182/blood-2006-05-021139.

Transplant recipients with intestinal graft-versus-host disease (GVHD) experience symptoms such as anorexia, nausea and vomiting, and diarrhea. Initial treatment is with oral prednisone, followed by a dose-tapering schedule to prevent relapse and allow recovery of the hypothalamic-pituitary-adrenal axis. Prednisone is associated with many side effects, some potentially serious. Oral beclomethasone dipropionate (BDP) was tested as a prednisone-sparing treatment for intestinal GVHD.

The randomized trial included 129 patients with gastrointestinal GVHD developing after allogeneic hematopoietic cell transplantation. All received a 10-day course of prednisone, followed by 50 days of treatment with oral BDP, 8 mg/d, or placebo. After 10 days, the patients underwent rapid tapering of prednisone while continuing BDP or placebo treatment. Rates of GVHD treatment failure—defined as worsening or recurrent GVHD requiring further immunosuppressive therapy—were compared between groups.

The 50-day treatment failure rate was significantly lower in the BDP group: hazard ratio (HR) 0.63 on intention-to-treat analysis. Analysis of patients eligible for steroid taper on day 10 also found a lower risk of treatment failure with BDP: HR 0.39 at 50 days and 0.38 at 80 days. At 200 days, there were 5 deaths in the BDP group versus 16 in the placebo group, HR 0.33. On analysis of 47 patients receiving unrelated or HLA-mismatched stem cells, BDP reduced mortality by 91%. At 1-year follow-

up, mortality remained significantly lower for patients randomized to BDP.

For patients with gastrointestinal GVHD, oral prednisone reduces the risk of relapse after tapering of prednisone. There is also a significant survival benefit, strongest in recipients of mismatched stem cells. Treatment benefit may result from limitation of gastrointestinal epithelial injury by GVHD, thus reducing the need for systemic glucocorticoids and the risk of serious infections.

Satwani P, Sather H, Ozkaynak F, et al: Allogeneic bone marrow transplantation in first remission for children with ultra-high-risk features of acute lymphoblastic leukemia: a Children's Oncology Group Study Report. Biol Blood Marrow Transpl. 2007;13:218-227.

Up to 30% of children with acute lymphoblastic leukemia (ALL) experience a relapse after treatment. Many relapses occur in patients at "standard" risk, but about 10% are in children with certain clinical and biologic factors associated with a very high relapse rate. A cooperative trial of allogeneic bone marrow transplantation (alloBMT) for children with such ultra-high-risk disease ALL in first relapse is reported.

The Children's Cancer Group study included 29 patients, median age 8.7 years, with ALL in first remission and one or more ultra-high-risk features. All enrolled children had a matched family allogeneic donor. Patients received conditioning therapy with fractionated total body radiation, 1,200 cGy; and cyclophosphamide, 120 mg/kg. This was followed by transplantation of unmobilized bone marrow. Methotrexate and cyclosporine were given for prevention of graft-versus-host disease (GVHD).

Grade II to IV acute GVHD developed in 20.7% of patients, while 3.7% had chronic GVHD. The condition regimen was well-tolerated, with just 1 treatment-related death. Mortality from progressive ALL was 35%. For the entire study group, 5-year event-free survival (EFS) was 58.6%. For patients without cytogenetic abnormalities, this figure increased to 77.8%. Just 20% of infants achieved 5-year EFS, compared with 66.7% of non-infants. Among patients positive for Philadelphia chromosome, 5-year EFS was 66.7%.

The results support a role of alloBMT for children with ALL and ultra-high-risk features. This strategy may be especially beneficial for children with primary induction failure and those positive for Philadelphia chromosome. The authors call for cooperative randomized trials to compare hematopoietic stem cell transplantation and intensive chemotherapy for children with ultra-high-risk ALL in first remission.

Ciceri F, Bonini C, Marktel S, et al: Antitumor effect of HSV-TK engineered donor lymphocytes after allogeneic stem cell transplantation. Blood First Edition Paper, prepublished online February 27, 2007; DOI 10.1182/blood-2006-05-023416.

New approaches are needed to take advantage of the antitumor effect of donor lymphocyte infusion after allogeneic hematopoietic stem cell transplantation (allo-HSCT) while avoiding the risk of graft-versus-host disease (GVHD). The authors have developed a polyclonal donor lymphocyte population that includes a "suicide gene" that selectively destroys the lymphocytes. The effects of the suicide gene thymidine kinase of herpes simplex virus (TK) were evaluated in patients with relapse of hematologic malignancies after allo-HSCT.

The experience included 23 patients with disease relapse after allo-HSCT from an HLA-identical sibling donor. The genetically engineered TK+ donor lymphocytes were produced under standardized conditions. Escalating infusions were given to define the optimal dose for antitumor activity; beginning with the twelfth patient, a single dose of 1×10^8 TK+ cells/kg was given. Outcomes of interest included engraftment of the genetically engineered lymphocytes, demonstration of the antitumor effect, and the effectiveness of ganciclovir in controlling GVHD.

Six patients died early or required early treatment for GVHD. Of the remaining 17 patients, all showed detectable circulating TK+ cells, starting a median of 18 days after infusion. Evidence of clinical benefit was achieved in 65% of patients, including a 35% complete remission rate and a 29% partial response rate. The greater the in vivo expansion of TK+ cells, the greater the antitumor effect. Ganciclovir eliminated the TK+ cells and provided an effective and selective treatment for GVHD in 7 patients. Seven patients treated with escalating infusions showed evidence of immunization against herpes simplex virus TK, but this did not preclude an antitumor effect.

The authors report the successful use of the TK "suicide gene" in a group of patients with relapse after all-HSCT. Clinical responses demonstrate the presence of an antitumor effect, closely related to the expansion of the TK+ cells. Clinical trials of this TK technology are already underway in several countries.

Shiras A, Chettiar S, Shepal V, et al: Spontaneous transformation of human adult non-tumorigenic stem cells to cancer stem cells is driven by genomic instability in a human model of glioblastoma. Stem Cells Express, published online March 1, 2007; doi:10.1634/stemcells.2006-0585.

Most human tumors show evidence of cancer stem cells (CSCs)—a subpopulation of cells with stem-cell-like characteristics. Studies of brain tumors have identified a CD133+/nestin+ population, suggesting that a normal neural stem cell (NSC) could be the cell of origin for gliomas. The authors report on their findings in cultured human NSCs, including their spontaneous transformation into CSCs.

The authors have previously reported the identification of human CD133+ NSCs from adult glioma tissue, including their long-term in vitro culture as "human neuro glial culture" (HNGC-1). In subsequent experiments, replicative senescence of HNGC-1 was associated with loss of genomic stability, leading to the emergence of a spontaneously immortalized cell line. This HNGC-2 line was found to have characteristics associated with CSCs, including the ability to renew themselves, to form CD133+ neurospheres, and to develop into high-grade, invasive brain tumors in immunodeficient mice. Like HNGC-1, the highly tumorigenic HNGC-2 cells expressed activated forms of Notch and Hes isoforms, which were significantly overexpressed in the brain tumor stem cells.

The development of a spontaneously immortalized brain tumor stem cell line from nontumorigenic human NSCs is reported. The findings highlight the critical role of genomic instability in the emergence of the transformed cells and their progression into tumorigenic CSCs. Further studies using the HNCG-1/HNGC-2 model could provide new insights into the pathways by which stem cells renew themselves, as well as their transformation into CSCs. Such studies might also lead to new chemotherapy regimens targeted against glioblastoma CSCs.

Managing the Myelodysplastic Syndromes Patient Through Transplantation

CME Assessment Test

1. What is the presumed mechanism of action of both decitabine and azacitidine?
A. Alkylating agent
B. Antimetabolite
C. Intercalating agent
D. DNA hypomethylating agent

2. A patient with which of the following cytogenetic abnormalities would be most likely to respond to lenalidomide?
A. 7q-
B. 5q-, 7q-, 21+
C. 21+
D. 20 q-

3. What is the most common side effect of lenalidomide?
A. Myelosupression
B. Nausea and vomiting
C. Diarrhea
D. Rash

4. What are the advantages of nonmyeloablative transplantation conditioning regimens?
A. Low toxicity
B. Low frequency of relapse
C. Low incidence of chronic graft-versus-host disease

5. What are the major risk factors for poor transplantation outcome in patients with myelodysplastic syndrome?
A. Marrow blast count
B. Complex cytogenetics
C. Comorbid conditons
D. All of the above

6. What measures have been successful in reducing the frequency of graft-versus-host disease after transplantation?
A. Removal of T-cells from the infused donor cells
B. Uuse of peripheral blood rather than marrow as a source of stem cells
C. The use of total body irradiation in preparation for transplantation

7. Which clinical factor is generally considered an important predictor of outcome for patients undergoing allogeneic stem cell transplantation for myelodysplastic syndrome?
A. Disease status at the time of transplantation
B. Age of the patient
C. IPSS risk group
D. performance status
E. All of the above

8. Allogeneic stem cell transplantation remains a mainly palliative approach for most patients with myelodysplastic syndrome.
A. True
B. False

9. "Mini-transplants" or "reduced-intensity transplants" refer to the use of smaller numbers of stem cells in the allografts in hope of reducing the expected graft-versus-host disease seen with full transplants.
A. True
B. False

CME Assessment Test Answer Sheet

Release Date: June 30, 2007 **Last Review Date: June 30, 2007** **Expiration Date: June 30, 2008**

Instructions

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

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

CME Evaluation Form

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

Overall Quality of the CME Activity	1	2	3	4	5
Articles in the publication were presented in a clear and effective manner.	1	2	3	4	5
The material presented was current and clinically relevant.	1	2	3	4	5
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 managing the myelodysplastic syndromes patient through transplantation, 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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