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REVIEWS

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## Multiple Choice Questions: Treatment Options for Multiple Myeloma and Myelodysplastic Syndromes

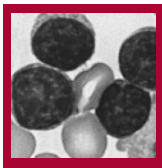
*John R. Wingard, MD, Editor*

The therapeutic prospects for multiple myeloma and the myelodysplastic syndromes have dramatically changed over the last two decades. The benefits of new therapies to our patients are unquestionable. Improved disease control has resulted in better quality of life, lessened morbidity, and in some cases fewer medical interventions and prolongation of survival.

An irony is that the pace of discovery has outraced our ability to sort through the various options (old and new) and order them according to their degree of effectiveness and toxicity. Moreover, the biologic variability of the disease states is considerable. Because treatment A is better than treatment B for one type of myelodysplastic syndrome does not mean it is superior in another type of myelodysplastic syndrome. A treatment that is great for refractory anemia may not be at all optimal for refractory anemia with excess blasts. The disease heterogeneity makes conduct of clinical trials difficult and application of the lessons of trials to clinical practice even more challenging.

Treatment selection is made even more difficult by individual patient factors, especially comorbidities. For example, a frail elderly person who struggles with ambulation due to arthritis could face severe threat from a regimen that causes neuropathy, even though that regimen may be more effective against multiple myeloma.

One could simplistically say that much of the dilemma one faces with these two diseases is "To transplant or not to transplant, that is the question." Actually, it is much more complicated, and treatment choice involves donor options, disease biology in a given patient, fitness of the patient, and timing. These are many of the questions addressed in the symposium held on February 14, 2009 at the BMT Tandem Meeting in Tampa, Florida. Many of the nuances of the multiple choices faced by both patients and clinicians are discussed in the proceedings of that symposium, described in this issue.



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Membership:

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## HRSA Panel Recommends Medicare Coverage for Transplants for MDS

The Health Resources and Services Administration (HRSA) Advisory Council on Blood Stem Cell Transplantation (ACBSCT) has endorsed the use of allogeneic transplantation for myelodysplastic syndrome (MDS). The council members will urge the Secretary of Health and Human Services to refer the issue to the Centers for Medicare and Medicaid Services (CMS) for review and consideration of a national coverage determination for transplant for MDS.

Claudio Anasetti, MD, then-ASBMT president-elect, presented the case for Medicare reimbursement at a recent advisory council meeting. He explained that hematopoietic stem cell transplantation (HSCT) is the only curative therapy for MDS; that 80% of MDS patients are 65 years or older; and that medicare reimbursement currently is allowed only after MDS has progressed to acute myeloid leukemia (AML), when transplantation is not as effective.

"Our senior patients are having to wait until their disease gets worse before Medicare reimbursement is available," he said.

Dr. Anasetti presented a preliminary report of a CIBMTR study of non-myeloablative HSCT in older patients with AML and MDS, and an ASBMT position statement based on an evidence-based review of HSCT for MDS. (The review and position statement appear in the February 2009 issue of *Biology of Blood and Marrow Transplantation*.)

The advisory council adopted the following policy:

- "MDS and AML are life-threatening blood disorders that are often part of the same disease process continuum.
- "There is strong evidence for the benefit of allo-HSCT in the treatment of AML.
- "There is strong evidence for the benefit of allo-HSCT for MDS in patients less than 65 years old, and growing evidence in patients older than 65 years.
- "There is also evidence that comorbidities may have a greater impact than age on allo-SCT outcomes in older adults.
- "Based on these findings, the ACBSCT endorses consideration for the use of allo-SCT for MDS and recommends that the Secretary instruct CMS, as a high priority, to develop an appropriate strategy for National Coverage Determination."

## New Brochure Promotes Careers in Blood and Marrow Transplantation

A brochure that recruits physicians and other health professionals to careers in blood and marrow transplantation is now available from ASBMT.

The brochure emphasizes that those entering the field do not have to choose between patient care, clinical investigations, and basic and translational research. All of these interests can be combined in BMT to make a significant impact on a rapidly evolving field of medicine.

Sections of the brochure address:

- the rapid growth and acceptance of BMT;
- a severe shortage of BMT personnel in the coming years;
- professional and personal BMT career benefits; and
- career development help that is available from ASBMT.

The recruitment brochure includes testimonials from physicians who recently entered careers in blood and marrow transplantation. For copies of the brochure, contact the ASBMT Executive Office.

## Anasetti Installed as ASBMT President; Weisdorf Elected Vice President

Claudio Anasetti, MD, has been installed as president of the American Society for Blood and Marrow Transplantation. He is a professor of oncology and medicine, and chair of the Blood and Marrow Transplant Department at the University of South Florida in Tampa.

Daniel J. Weisdorf, MD, professor of medicine at the University of Minnesota in Minneapolis, is the newly elected and installed vice president, to become president in 2011. He also is the director of the University of Minnesota's Adult Blood and Marrow Transplant Program, the scientific director for the National Marrow Donor Program, and a senior research advisor for the CIBMTR.

Installed as treasurer was Stephanie J. Lee, MD, MPH, an associate professor of medicine at the Fred Hutchinson Cancer Research Center in Seattle.

Newly elected and installed directors are Karen Ballen, MD, of Harvard Medical School and Massachusetts General Hospital in Boston; James L. Gajewski, MD, of Oregon Health & Science University, Portland; and James W. Young, MD, of Weill-Cornell Graduate School of Medical Sciences and Memorial Sloan-Kettering Cancer Center in New York.

A. John Barrett, MD, was elevated to president-elect and will assume the presidency in 2010. He is section chief for stem cell allotransplantation in the Hematology Branch of the NIH National Heart, Lung and Blood Institute, Bethesda, Maryland.

## Physician Assistants, Nurse Practitioners form New Special Interest Group

A special interest group for "mid-level practitioners" has been established within ASBMT.

Created to address the unique professional needs of the physician assistant (PA) and the nurse practitioner (NP), the new special interest group (SIG) will develop sessions for the annual BMT Tandem Meetings and will have a role in society committees.

A steering committee has announced the SIG's initial goals:

- Develop a day or day-and-a-half educational track at the 2010 BMT Tandem Meetings;
- Create a core curriculum for NPs and PAs;
- Establish a list-serve for mid-level practitioners;
- Conduct a needs assessment; and
- Recommend nominees for relevant ASBMT committees.

Membership in the SIG is open to any ASBMT member. PAs and NPs can join ASBMT as Affiliate Members, with $125 annual dues that includes a subscription to *Biology of Blood and Marrow Transplantation*.

A recruitment campaign is underway. PAs and NPs interested in learning more or joining the SIG are invited to contact the ASBMT Executive Office.

## ASBMT Membership Grows to Record 1533

ASBMT membership has reached 1533, continuing 12 consecutive years of growth. The active Member category achieved the largest increase last year, growing at an annual rate of 5 percent.

Health professionals outside the United States and Canada make up 15 percent of ASBMT members.

ASBMT

Blood and Marrow TRANSPLANTATION REVIEWS

# Symposium Report

## The Hematology Circle: Optimizing Pretransplant Induction Regimens for Multiple Myeloma and Myelodysplastic Syndromes

Adapted from a continuing medical education symposium presented at the 2009 BMT Tandem Meetings on February 14, 2009, in Tampa, Florida. This program is supported by an educational grant from Celgene.

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### Overview

The rapid clinical development of novel therapies to treat Multiple Myeloma (MM) and Myelodysplastic Syndromes (MDS) has generated several educational gaps concerning the use of these agents as induction therapy when transplant is being considered. The objective of this activity is to provide practical information on selection of optimal pretransplant induction regimens for MM and MDS. *The Hematology Circle* program is designed to have maximum impact on bridging the identified educational gaps to improve knowledge, competence, and performance.

### Target Audience

This activity is intended for transplantation physicians and allied health professionals.

### Learning Objectives

- Identify patients with MM and MDS who should be considered for transplant by synthesizing current data on molecular prognostication and novel therapeutic approaches
- Select optimal pretransplant induction therapies for MM and MDS based on prognostic risk, therapeutic efficacy, therapeutic toxicity, and preexisting comorbidities
- Define considerations for stem cell harvest following induction therapy with novel agents

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

### Disclaimer

This material has been prepared based on a review of multiple sources of information, but it is not exhaustive of the subject matter. Participants are advised to critically appraise the information presented, and are encouraged to consult the above-mentioned resources as well as available literature on any product or device mentioned in this program.

### Disclosure of Unlabeled Uses

This educational activity may contain discussion of published and/or investigational uses of agents that are not approved by the US Food and Drug Administration. For additional information about approved uses, including approved indications, contraindications, and warnings, please refer to the prescribing information for each product, or consult the Physician's Desk Reference.

### Faculty Disclosure

Consistent with the current Accreditation Council for Continuing Medical Education policy, the CME 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 CME Provider has a mechanism in place to identify and resolve any conflicts of interest discovered in the disclosure process. The presenting faculty members have all made the proper disclosures, and the following relationships are relevant:

Sergio A. Giralt, MD, has received honoraria from Celgene Corporation, Genzyme Corporation, Millennium Pharmaceuticals, Inc., and Novartis and is on the Speakers Bureaus for Celgene Corporation, Genzyme Corporation, Millennium Pharmaceuticals, Inc., and Novartis.

William I. Bensinger, MD, has received honoraria from Celgene Corporation and Millennium Pharmaceuticals, Inc., and is on the Speakers Bureaus for Celgene Corporation and Millennium Pharmaceuticals, Inc.

Michael W. Schuster, MD, has received honoraria from Celgene Corporation, MGI Pharma, Inc., and Millennium Pharmaceuticals, Inc.; is on the Speakers Bureaus for Celgene Corporation and Millennium Pharmaceuticals, Inc.; and is on the Advisory Board for Celgene Corporation and MGI Pharma, Inc.

## Introduction

*Sergio A. Giralt, MD*

We are in an exciting time in the exploration of therapeutic options for multiple myeloma (MM) and myelodysplastic syndromes (MDS). Important progress is being made in the treatment of these diseases, for which in the past the prognoses has been grim.

Promising new agents are now available, but their use is accompanied by the challenge of selecting the most appropriate care for each individual patient. For example, in the era of effective immumodulatory drugs and proteasome inhibitors, what is the optimal induction therapy for patients eligible for allogeneic stem cell transplantation, still the only curative option for MM and MDS? Given the effectiveness of novel treatment regimens, should patients who achieve a complete response with these therapies always proceed to transplantation? What about a 56-year-old MDS patient who achieves a complete remission on a novel agent such as azacitidine? Should this patient undergo transplantation or continue maintenance therapy? If maintenance therapy is chosen, how long can azacitidine be continued safely and how long will it be effective? For a patient with a suitable donor awaiting transplantation, what treatment should be administered in the meantime, or is observation sufficient?

The following articles provide case presentations for both MM and MDS patients. Unfortunately, however, this process will do more to raise questions than to provide definitive answers. The authors do, however, provide some of the most recent data from ongoing clinical trials with the hope that this information will enable clinicians and their patients to make informed choices and to be part of the process leading to the discovery of effective treatments for these hematological malignancies.

Looking to the future, bone marrow transplantation clinical trial networks and cooperative groups have started an initiative of doing large national studies to look at the important questions related to treatment optimization. We have been successful in finishing a trial of autologous reduced-intensity allogeneic transplantation versus double autologous transplantation in MM, and we hope the data from this trial will be analyzed next year. Another study in progress is investigating the use of maintenance therapy with lenalidomide versus observation in MM. This study will be fully accrued toward the middle of this year, and we hope to have useful data in the next couple of years.

The next study that is planned will look at consolidation treatment. There is a lot of discussion of early versus late transplantation and of randomization in patients who have had major responses. It is felt that the number of patients needed for such a study is enormous, so an issue that a large group of physicians, thought leaders, and even patient advocates are trying to address is the best approach to consolidation treatment in the era of novel therapies. In this study, patients with newly diagnosed MM will be registered and randomized after one autologous transplantation to receive either no consolidation therapy but instead go to lenalidomide maintenance alone; to receive 4 cycles of consolidation with lenalidomide, bortezomib, and dexamethasone; or to get a second autologous transplant with high-dose melphalan therapy and then go on to lenalidomide maintenance.

For patients with MDS it may be time to think about a large trial looking at induction with hypomethylating agents prior to stem cell transplantation. As with MM, for MDS ablative induction with standard drugs has not been shown to have an important impact on outcomes, but with more effective induction regimens that are less toxic, the question of the effect of induction on outcomes continues to be raised, particularly because the results of transplantation for MDS patients are not particularly good, and relapse continues to be a problem.

Another concern in MDS patients whose disease has not progressed to acute leukemia is that Medicare may not pay for hypomethylating agent treatment to induce induction or for transplantation. In addition to making treatment prohibitive, this problem will make it difficult to acquire study patients. So although the medicine and the science support ongoing studies in older patients who have government-based insurance in the United States, the lack of funding for these treatments may prohibit investigation.

We hope that the information presented in the following reports will be useful to clinicians treating patients with MM and MDS and that they will become active advocates for additional research to address these unanswered questions.

## Optimizing Transplantation Outcomes in Multiple Myeloma

*William I. Bensinger, MD*

### INTRODUCTION

Multiple myeloma (MM), a B-cell hematologic malignancy involving plasma cells, is curable only with allogeneic stem cell transplantation (SCT), which exerts a graft-versus-myeloma effect. Significant improvements in survival for MM patients are now possible, however, owing to the introduction of novel drugs, including alkylators, steroids, anthracyclines, immunomodulatory drugs, and proteasome inhibitors (Table 1). For patients who are suitable candidates, high-dose chemotherapy with autologous SCT after induction therapy has been shown to improve response rates, progression-free survival, and overall survival compared with conventional chemotherapy. Thus, induction strategies have rapidly changed to incorporate drugs such as thalidomide, lenalidomide, and bortezomib. These drugs have been combined with corticosteroids, alkylators, and anthracyclines for front-line treatment of patients with MM. Preliminary phase I and phase II studies have indicated very high response rates and complete-response (CR) rates formerly seen only with allogeneic SCT. Emerging data from randomized trials suggest that older regimens such as VAD (vincristine, Adriamycin, and dexamethasone) are not as effective for induction as newer combinations and that novel drug combinations for induction translate into improved progression-free survival. Thus, new regimens incorporating novel agents should

**Table 1. Drugs for Multiple Myeloma**

| Class | Drugs |
|---|---|
| Steroids | Dexamethasone, prednisone |
| Alkylators | Cyclophosphamide, melphalan, bendamustine |
| Anthracyclines | Doxorubicin, pegylated liposomal doxorubicin |
| Immunomodulatory drugs | Thalidomide, lenalidomide |
| Proteasome inhibitors | Bortezomib |

improve overall response rates and increase the numbers of complete responders, leading to improved overall survival [1,2].

## NOVEL-AGENT INDUCTION REGIMENS FOR MM

Given the availability of newer, more effective drugs for treatment of MM (Table 1), determining how to optimize their effectiveness is a work in progress. In particular, although many new drugs have shown possible benefits for induction therapy prior to transplantation (Table 2), we are still learning the best way to use these drugs to optimize transplantation outcomes.

### *Bortezomib and Dexamethasone*

The focus on induction strategies in the treatment of MM is a new phenomenon. Until recently, no one had shown the importance of the type of induction regimen used in MM patients prior to transplantation, but we now have some promising data from the French Francophone Myeloma Intergroup (IFM) on the use of VAD versus 2-drug (doublet) induction with bortezomib and dexamethasone in patients with newly diagnosed MM. Patients who achieved less than a very good partial response (PR) after transplantation were offered a second transplant. This study is fully enrolled, and an update presented by Harousseau et al at the American Society of Hematology 2008 meeting in San Francisco (ASH 2008) showed that with induction therapy, the bortezomib-dexamethasone regimen was significantly better across all response points; from a CR to a very good PR or better, induction with bortezomib-dexamethasone was superior [3]. When patients went to transplantation, whether it was by intention to treat or the patients actually underwent transplantation, the patients who received bortezomib-dexamethasone induction had significantly higher response rates. The major response rates were a very good PR or better, and they were all significantly better than with VAD induction. Therefore, at least at this point in time, VAD induction is less effective for such patients who are going on to transplantation, and this effect carries through throughout the transplantation process.

### *Bortezomib, Dexamethasone, and Thalidomide*

Over the last few years, thalidomide-dexamethasone (TD) has been one of the most commonly used induction regimens for the treatment of newly diagnosed MM. An ongoing, partially accrued trial by the Italian Myeloma Network (GIMEMA) cooperative is investigating the use of triplet therapy with bortezomib, thalidomide, and dexamethasone, compared with a doublet novel-agent sequence of TD. Patients then go on to tandem transplantation, with an induction-treatment crossover to TD if they had undergone induction with bortezomib (Velcade), thalidomide, and dexamethasone (VTD), or to VTD if they had undergone induction with TD.

The preliminary results presented at ASH 2008 [4,5] showed a much higher response rate with the triplet VTD regimen compared with the doublet TD regimen, with VTD-treated patients having a superior response rate across all categories. After transplantation, the rates for PR and for CR and near-CRs were much higher for patients who got the VTD induction therapy.

## INDUCTION THERAPY AND PROGRESSION-FREE SURVIVAL

Other very interesting new data presented at ASH 2008 from the IFM trial showed significantly better progression-free survival in patients who received induction therapy with bortezomib-dexamethasone than in those who received VAD [3]. Similarly, data presented from the Italian Myeloma Network study showed significantly better progression-free survival for the triplet of VTD compared with TD [4]. The importance of these data must be emphasized because until now we have had no real data showing that the type of induction therapy mattered for patients going on to undergo transplantation. We can now say, at least at this point, that progression-free survival is improved by better induction therapies (Figure). Overall survival is not yet better, but the follow-up for these studies is still fairly early, with only about 2 years of follow-up, and the Italian trial is only halfway accrued.

Another trial reported at ASH 2008, by Sonneveld et al [6], looked at bortezomib-based induction compared with either TD or VAD. According to these data, transplantation improved responses in patients who had received traditional induction therapy with VAD or novel induction therapy, but patients who received novel induction therapy with bortezomib-dexamethasone or VTD had a better initial response that carried through the transplantation process.

## LENALIDOMIDE AND DEXAMETHASONE

The immunomodulatory drug lenalidomide has single-agent activity against MM and additive effects when combined with dexamethasone [7]. Unfortunately, venous thrombotic events are a common complication of therapy with regimens of lenalidomide plus dexamethasone and may adversely affect the survival of patients with newly diagnosed myeloma who receive this therapy. This problem was investigated by the Eastern Cooperative Oncology Group in a large trial that looked at high-dose versus low-dose dexamethasone combined with lenalidomide, in which the patients in both treatment arms received lenalidomide. Earlier data showed that even though patients who received the higher dose of dexamethasone had a better overall response rate, these patients experienced more deep-vein thrombosis and infectious complications and had a higher early-death rate. After the first 264 patients were enrolled, the trial was amended to require mandatory thromboprophylaxis with aspirin for all patients, with a recommendation to use stronger thromboprophylaxis with either warfarin or low molecular weight heparin for patients receiving high-dose dexamethasone. According to recent data reported at ASH 2008, the survival rate is 75% in both treatment arms after 3 years of follow-up [8].

**Table 2. Induction Regimens for Multiple Myeloma**

- Doublets
  - Thalidomide/dexamethasone
  - Bortezomib/dexamethasone
  - Lenalidomide/dexamethasone (high versus low)
- Triplets
  - Vincristine/Adriamycin/dexamethasone (traditional agents)
  - Bortezomib/thalidomide/dexamethasone
  - Bortezomib/lenalidomide/dexamethasone
  - Bortezomib/doxorubicin/dexamethasone
- Quadruplets
  - Promising future therapies?

Patients in both treatment arms who went off therapy after 4 cycles and then went on to transplantation had a 92% survival rate at 3 years, whereas patients who continued therapy had only a 79% survival rate at 3 years; however, the comparability of these data is questionable because this trial was not randomized because patient and physician preferences played a role in decisions regarding the duration of therapy. The patients who underwent transplantation may have been younger, but they may also have had suboptimum responses to induction. Nevertheless, these data do indicate that after lenalidomide-dexamethasone induction, transplantation produces very good outcomes at 3 years.

Another concern with lenalidomide is stem cell toxicity and its possible effect on cell mobilization after induction. Investigations have looked retrospectively at the ability to mobilize stem cells in patients with lenalidomide-based regimens. There are data suggesting that, in general, the collections are less robust if granulocyte colony-stimulating factor induction alone is used for mobilization, but this problem can be overcome with chemotherapy, primarily with cyclophosphamide-based regimens.

## CLINICAL DECISION MAKING: A CASE REPORT

The clinical characteristics of a patient with an initial presentation of MM are summarized in Table 3. This patient exemplifies factors that may affect the choice of individualized treatments for MM patients.

The patient is a 48-year-old lumberyard worker who presented to the emergency department with pneumococcal sepsis and pneumonia, as well as other findings (Table 3). Unfortunately, cytogenetic analyses were not performed at his initial presentation.

Traditionally, induction treatment for MM patients was limited to VAD. With the availability of new classes of drugs, particularly immunomodulatory drugs and the proteasome inhibitors, the most important question is how to best use these therapies for induction. We have several bortezomib-based induction regimens that look promising, at least in phase I and II studies. These options include using doublets with TD, bortezomib-dexamethasone, or lenalidomide-dexamethasone. Recent data indicate that a triplet regimen may be better, and it is possible that 4-drug regimens will be even more effective.

What if the patient presented with an elevated creatinine concentration of 2.8 mg/dL, suggesting possible renal disease? In patients with renal failure, bortezomib is acceptable because it does not require dose adjustment. With dose adjustment, lenalidomide can also be used for induction in patients with renal failure.

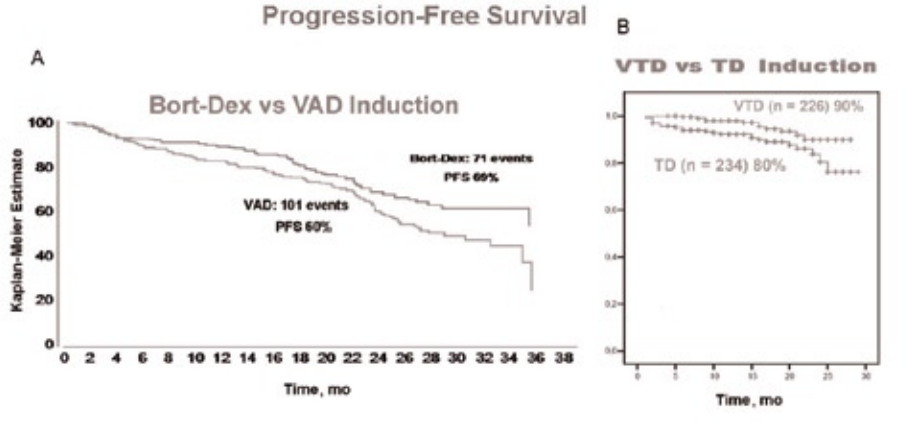
What if the patient had diabetes with neuropathy on presentation, would this change your recommendations? For patients with diabetes, the data are too limited to recommend, for example, induction based on bortezomib and anthracycline over a regimen of bortezomib and dexamethasone or of lenalidomide and dexamethasone.

Caution is required in patients with preexisting neuropathies. Thalidomide or bortezomib should be avoided or used only with very careful monitoring of how the patient tolerates these agents. Anthracyclines must be used with caution in patients with cardiac disease.

Going forward, suppose that this patient receives induction therapy with the triplet of VTD and that he is reassessed and found to have a near-CR. He is scheduled to go to undergo autologous SCT, but he wants to discuss his options with you. Given that the patient has achieved a near-CR, should he undergo transplantation or not? Should he undergo a tandem autograft? Or, is transplantation optional, given that the patient can proceed to consolidation with lenalidomide, dexamethasone, and bortezomib or can continue maintenance therapy with thalidomide?

The arguments in favor of transplantation are that although CR is a positive prognostic marker for survival and these novel new drugs are available, they may not produce a remission as durable as the remission achieved with autologous SCT. We know that novel drugs are very effective in high-risk patients and high-risk disease and that they may eliminate these high-risk cells, but as of now we really have no data to show that these novel induction therapies alone are as effective as autologous transplantation after induction therapy. Thus, autotransplantation may further improve remission durability, and recent response data certainly indicate this supposition to hold true with autotransplantation performed after induction therapy with novel drugs. Large clinical trials are needed to examine this question, and they would be an important way to answer it.

Data from prior IFM studies in which patients received primarily VAD-based or




**Induction regimen affects progression-free survival (PFS) in multiple myeloma. New data from the French Francophone Myeloma Intergroup (A) demonstrated significantly better PFS in patients who received induction therapy with bortezomib-dexamethasone (Bort-Dex) compared with those who received traditional therapy with vincristine, Adriamycin, and dexamethasone (VAD) [4]. Similarly, data presented from the Italian Myeloma Network study (B) showed significantly better PFS for the triplet of bortezomib (Velcade), thalidomide, and dexamethasone (VTD), compared with thalidomide and dexamethasone (TD) [4]. The importance of these data must be emphasized, because until now we have had no real data showing that the type of induction therapy mattered for MM patients going on to undergo transplantation. Adapted from [4,5].**

**Table 3. Multiple Myeloma Case Patient***

| |
|---|
| Patient characteristics |
| 48-Year-old man, lumberyard worker |
| In September 2003, admitted to emergency department with pneumococcal sepsis and pneumonia. |
| X-ray showed multiple lytic bone lesions. |
| Monoclonal peak of 5.3 g/L (IgG κ) |
| Hemoglobin, 8 g/dL |
| Creatinine, 1.8 mg/dL |
| Normal calcium levels |
| 2-Microglobulin, 5.6 mg/L; albumin, 3.0 g/dL |
| Marrow 60% plasma cells; cytogenetic analysis not done |
| Options for induction therapy |
| Thalidomide/dexamethasone |
| Bortezomib/thalidomide/dexamethasone |
| Lenalidomide/high-dose dexamethasone |
| Lenalidomide/low-dose dexamethasone |
| Bortezomib/dexamethasone |
| Other? |
| Would the following situations modify recommendations about treatment? |
| The patient's creatinine was 2.8 mg/dL on presentation. |
| The patient had diabetes mellitus with moderate neuropathy on presentation. |

*IgG indicates immunoglobulin G.
Oncol. 2008;26:(May 20 suppl). Abstract 8516.

thalidomide-based induction regimens indicated that patients who achieved a CR had much better survival rates than patients with lesser degrees of response, again supporting the idea that getting a CR is a good surrogate marker for increased survival [9].

What are the disadvantages of transplantation? Several trials have performed post hoc analyses to examine patient outcomes after they undergo 1 versus 2 transplantations. Such analyses have shown that patients who achieve a major response, ie, a very good PR or better, do not benefit from a second transplantation procedure. How do novel drugs fit into this scenario? The argument is that in patients who have much better responses to novel drugs, high-risk cells are eliminated, making transplantation optional or superfluous. In addition, data indicate that high-risk patients with cytogenetic and other risk factors tend to benefit less from autologous SCT.

The Mayo Clinic retrospectively compared patients who achieved a CR with induction with patients who did not but who then went on to transplantation and to achieve a CR after transplantation [10]. The data show that if patients achieve a CR they do not seem to benefit from autologous SCT. The caveat, however, is that these data were obtained from patients who received the older induction regimens based primarily on VAD. The other important point is that we do not know what would have happened to the patients who achieved a CR if they had not undergone transplantation. We know that they don't do any better with transplantation, but we don't know if they might have done significantly worse had they not undergone transplantation. Again, this result speaks to the possibility that a greater depth of remission can be achieved with autologous SCT.

We know from several studies that high-risk patients have as good or, in many cases, better responses to the novel drug therapies. Data from the Italian study that evaluated patients with deletion 13 or 4;14 chromosomal abnormalities showed that those patients who received induction therapy with the triplet of VTD had more-robust major responses, including CR or near-CR [11]. Because follow-up data are lacking for these patients who underwent transplantation, however, we do not know whether the high-risk patients in these studies who then underwent transplantation had a better outcome. Data relating to this issue have been reported for a study that used a total-therapy approach that applied all active treatment ingredients up front, with the objective of maximizing long-term disease control [12]. Patients received induction with thalidomide, dexamethasone, cisplatin, doxorubicin, cyclophosphamide, and etoposide for 2 cycles, underwent tandem transplantation, and then received TD as maintenance throughout their treatment course. In addition, the patients received thalidomide, dexamethasone, cisplatin, doxorubicin, cyclophosphamide, and etoposide intensification after transplantation. The 2-year survival rate for these patients was very good at 87%, and the low-risk patients did quite well. The high-risk patients, however, had an inferior survival rate of 70%, and their event-free survival rate at 2 years was only 58%. Therefore, even with these novel induction therapies in tandem transplantation, high-risk patients appear to remain at high risk, as indicated by their outcomes.

## SUMMARY

We now have more effective induction regimens, which translate into improved responses and higher progression-free survival rates following high-dose therapy and transplantation. The early data suggest that triplet therapy regimens are better than doublet regimens. Current data also suggest that VAD induction is definitely inferior to induction therapy with newer agents. The role of doublet induction with lenalidomide is somewhat less clear because of the lack of good comparison trials; however, preliminary findings of 92% survival rates at 3 years indicate that lenalidomide is an acceptable and promising induction therapy.

Given the effectiveness of new, novel treatments, a concern faced by patients and physicians is the decision of whether to proceed to transplantation once a CR is achieved. At present, however, we have no data to indicate that these patients should not go on to transplantation. Further investigation is required to determine the role of transplantation after induction therapy that leads to CR. Particularly informative would be a large study in which patients who achieve a CR are then randomized to receive transplantation or maintenance therapy; the outcomes could then be compared. Patients in poor-risk groups seem to respond well to novel drugs, but the impact on survival remains unclear at the present time.

Regarding the case patient we presented earlier, he underwent a single autologous transplantation in November 2004. He tolerated the treatment well and declined maintenance treatment. When he was seen for follow-up 2 years later he was doing well, having remained in remission for 2 years. Patients such as this man remind us of the importance of ongoing efforts to improve treatments to preserve and enhance life in the face of serious diseases such as MM.

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# Optimizing Transplantation Outcomes in Myelodysplastic Syndromes

*Michael W. Schuster, MD*

Myelodysplastic syndromes (MDS) can be cured only by allogeneic bone marrow transplantation. In eligible patients with suitable donors, effective new drug therapies must be considered during the treatment process surrounding allogeneic transplantation. Improvements in treatment provide new hope for MDS patients but also challenge patients and clinicians to make difficult decisions among a complex array of therapeutic options.

## Patient Scenarios: Case Reports

The situations that might be encountered and some of the questions that we must attempt to answer in dealing with patients with MDS are exemplified by 2 typical case patients (Table 1). The first patient, a 61-year-old woman with a history of breast cancer, has secondary MDS with a 6,9-translocation with ringed sideroblasts, a cytogenetic abnormality that is seen in acute myeloid leukemia (AML) and rarely in MDS. There was a time when this diagnosis was considered fatal, with the only treatment options being supportive care with transfusions. Today the scenario for a patient like this may be very different. Suppose this patient has a sibling, an older sister, 65 years old, who is a perfect match, and while we are preparing the patient for transplantation, we begin therapy with decitabine and she achieves a complete remission.

The question is what to do next? Do we proceed directly to transplantation? Do we continue with decitabine for a total of 4 cycles? Do we continue decitabine until the patient relapses? Or do we treat this patient in some other way?

The second case patient is younger, a 40-year-old man, a chemical engineer with a strong exposure history who presented with pancytopenia and trilineage dysplasia with 10% blasts. Cytogenetic analysis reveals deletion 7. Like the first patient, this patient is also is fortunate enough to have a sibling donor and is seeking a second opinion regarding stem cell transplantation. Should this patient proceed directly to myeloablative transplantation or should he undergo reduced-intensity transplantation? Is induction therapy important in a patient like this to reduce the blast count? Should he be treated with a new agent such as azacitidine?

## Transplantation in MDS: Patient Eligibility and Outcome Optimization

Patient assessment in MDS includes identification of comorbidities as well as prognostic scoring of MDS by use of the International Prognostic Scoring System (IPSS) and the WHO Prognostic Scoring Systems (Table 2) [1]. Uncertainty remains, however, as to how the results of the assessment process may be used to determine patient suitability for transplantation. Once the decision is made to proceed to transplantation, questions must be considered regarding the conditioning regimen itself, because several options are available. These include fully myeloablative and reduced-intensity regimens. Whether or not to provide pretransplantation chemotherapy is another consideration.

The best time to perform transplantation is another issue requiring careful consideration. Morbidity and mortality associated with the transplantation process itself must be addressed, particularly graft-versus-host disease, a problem faced by all transplantation patients and their caregivers. Another concern is the availability of viable treatment options in the unfortunate but all too common event of relapse following transplantation.

## Comorbidities and Transplantation Outcomes

A very interesting presentation at the American Society of Hematology (ASH) 2008 annual meeting addressed the impact on overall survival of comorbidities related to nonleukemic death in MDS patients [2]. This

investigation was carried out in 2 phases. First, in a learning phase, more than 800 MDS patients at the University of Pavia in Italy were studied to determine some of the most important comorbidities leading to nonleukemic mortality in MDS. Interestingly, cardiac disease correlated with iron overload was the most prevalent fatal comorbidity. Other important comorbidities associated with nonleukemic death were moderate/severe hepatic disease, severe pulmonary disease, renal disease, and solid tumors. The finding of high nonleukemic cardiac mortality associated with iron overload raises the issue of using agents to treat iron overload in MDS patients, although at this time data are not available to show the impact of such agents on survival. After the identification of a number of comorbidities in the 800 patients, the second phase of the study was performed in a validation cohort comprising of more than 500 patients in Germany. The findings in the German cohort validated exactly what was seen in 800 Italian patients, that patients with low-risk comorbidity status had a very good prognosis, whereas those with high-risk comorbidiy had a much worse prognosis. And again, cardiac issues played a major role. So in considering the eligibility of MDS patients for transplantation, we must look at comorbidities not only for predicting transplantation outcome but also because of the risk of nonleukemic death attributable to comorbidity in MDS patients.

## IPSS Score and Transplantation

A study by Cutler et al [3] published more than 5 years ago, looked at the association of survival rates with IPSS scoring in MDS patients, specifically to answer the question of whether delaying transplantation had a better or worse impact on patients depending on their IPSS score. What we have come to realize is that patients with low and intermediate-1 risk MDS are better served by delaying transplantation, and that there actually is loss of life if these patients go immediately to transplantation. These outcomes are very different from those of patients with intermediate-2 or high-risk MDS, in whom there are years of life saved by proceeding directly to transplantation. Thus delaying transplantation saves lives in patients with low or intermediate-1 MDS, whereas delaying transplantation risks loss of life in patients with intermediate-2 or high-risk disease.

**Table 1. Case Patients with Myelodysplastic Syndrome (MDS)**

MDS Case #1

- 61-Year-old woman with history of breast cancer
- Received x-ray therapy and cyclophosphamide, methotrexate, and fluorouracil after mastectomy
- Presents with fatigue; found with hemoglobin of 7.1 g/dL, absolute neutrophil count of 1000/mL, platelets 41,000/mL
- Bone marrow: 5% blasts, trilineage dysplasia
- Cytogenetics: t(6,9)
- 1 HLA-matched 65-year-old sibling

Begins therapy with decitabine and achieves a complete remission

What would you do next?

1. Proceed to transplantation
2. Continue on decitabine therapy for a total of 4 cycles
3. Continue on decitabine therapy until relapse
4. Other

MDS Case #2

- 40-Year-old male chemical engineer with strong history of exposure
- Presents with bruising
- Hemoglobin 10.9 g/dL, platelets 32,000/mL; white blood cells 3200/mL with 50% neutrophils, 2% blasts
- Bone marrow: 10% blasts, trilineage dysplasia
- Cytogenetics: deletion 7
- Has sibling donor

Comes for a second opinion regarding role of induction therapy prior to stem cell transplantation.

What would you do next?

1. Proceed to transplant—myeloablative conditioning
2. Proceed to transplant—reduced-intensity conditioning
3. Attempt to reduce blast count with induction therapy
4. Other

## Effect of Related versus Unrelated Donors

A number of groups of investigators have looked at the impact of donor characteristics on transplantation outcomes in MDS patients. A European research group looked at allogeneic transplantation with matched related and unrelated donors and observed good overall 5-year survival, with no significant difference in outcome between patients with matched related donors and those with matched unrelated donors. So if a patient who is a good candidate for transplantation has a matched unrelated donor, there is no reason for hesitation in pursuing this potentially curative treatment option.

## Myeloablative versus Reduced-Intensity Induction Regimens

Lim et al, on behalf of the MDS Subcommittee, Chronic Leukemia Working Party of the European Blood and Marrow Transplantation Group, looked at the issue of standard myeloablative regimens versus reduced-intensity regimens in patients who were older than 50 years (median age 56 years) and who underwent allogeneic stem cell transplantation. The investigation included cases representing the full spectrum of MDS scored by use of the French-American-British classification system [5]. Significant findings from multivariate analysis were that disease stage at time of transplantation had an important prognostic impact on outcomes, and the use of reduced-intensity conditioning was associated with higher relapse rates but lower transplantation-related mortality. Overall survival in patients who received reduced-intensity conditioning was comparable to that of patients who received standard myeloablative conditioning. And although patients older than 60 years had increased relapse rates, there was no significant difference in overall survival in these older patients compared with patients aged 50-60 years. Note that these findings regarding factors affecting transplantation are specifically applicable the case patients described in Table 1.

## Hypomethylating Agents in MDS Treatments

We now have many ways to treat MDS patients. The hypomethylating agent azacitidine has been in use for a number of years and is definitely associated with a survival advantage. In a large study, several hundred patients were treated with 1 of 3 conventional care regimens: low-dose cytosine arabinoside,

**Table 2. Considerations in Allogeneic Stem Cell Transplantation (SCT) for Myelodysplastic Syndrome (MDS)**

| |
|---|
| Pretransplantation comorbidities significantly impact outcome |
| Best response seen in low/intermediate-1 risk MDS with <5% blasts |
| 65%-75% 3-year-survival with HLA-matched donor |
| Conditioning regimen |
| Myeloablative versus reduced-intensity/nonmyeloablative |
| Pretransplantation chemotherapy |
| Transplantation-related morbidity and mortality |
| Increases with age |
| ≤25%-30% even in favorable groups |
| Posttransplantation relapse |
| 10%-40% in intermediate-2/high risk patients with ≥5% blasts |
| Graft-versus-host disease remains the most frequent complication post SCT |

intensive induction chemotherapy, or best supportive care such as transfusions. The outcomes for these patients were compared to those for patients who were treated with azacitidine. Results showed that median survival and 2-year overall survival favored the azacitidine group, and in this particular study there was not a significant difference in need for supportive care with transfusions for those patients. Kaplan-Meier analysis also showed significantly better overall survival in the patients treated with azacitidine.

Investigations of patient characteristics showed a benefit favoring the azacitidine group for all types of MDS patients: patients who were older or younger, patients with MDS of various French-American-British classifications, and patients whose MDS was low risk or high risk according to IPSS. The challenge now is to answer questions regarding the long-term use of azacitidine. Although many patients have a very good early response to azacitidine, the best response rates in some patients took longer to achieve, and in some cases achieving complete response took a number of months. Thus long-term treatment with azacitidine may be a very good option for some MDS patients. It is important not to stop azacitidine treatment too soon, because responses may continue for quite a number of months. And maintenance therapy with azacitidine might be a very useful way of treating MDS patients.

At the ASH 2008 annual meeting, Silverman et al [7] presented an update of the Cancer and Leukemia Group B study, an international, phase III, multicenter trial that has demonstrated that azacitidine is the first treatment to significantly extend overall survival in higher-risk MDS patients. The most recently presented results show that although many patients achieve a hematologic response with azacitidine in early treatment cycles, continued azacitidine treatment can further improve patient responses. In this study, patients received a median of 9 treatment cycles of azacitidine (range 1-39 cycles). For those achieving a response of hematologic improvement or better (partial or complete response), 90% did so by 9 treatment cycles, and 40% of responders achieved an improved response even later. These results indicate that unless patients suffer unacceptable toxicity or disease progression, continued treatment with azacitidine is appropriate and may maximize patient benefit [7].

Interestingly, however, the results of investigations of azacitidine treatment are not completely clear. Grövdal et al [8] for the Nordic MDS Group also presented updated results at the ASH 2008 annual meeting, in this case for a prospective multicenter phase II study designed to assess the clinical feasibility and utility of long-term maintenance treatment with azaciditine. In this randomized study patients were given azacitidine maintenance following induction chemotherapy. Although there was a complete response rate in those patients, only 17% of patients maintained their complete response at greater than 2 years [8]. These results suggest that patients with remission induced with a hypomethylating agent may benefit from transplantation before 2 years, because a drop-off in effectiveness may occur at 2 years.

Another hypomethylating agent used in MDS patients is decitabine, a drug that is under investigation in several studies presented at the ASH 2008 annual meetings. One of these, a prospective, open-label, phase II multicenter study by Cashen et al [9] looked at the use of decitabine in a population of elderly patients (median age 74 years) with AML. Patients in this study were treated with an outpatient regimen similar to regimens now being used commonly across the country, 20 mg/m2 on days 1 to 5 every 4 weeks. These patients did quite well, with a complete response (CR) rate of approximately 25% [9]. Blum et al, looking at single-agent decitabine treatment in acute myeloid leukemia patients older than 70 years, saw similar results, with a CR rate of 50% [10].

Continued use of decitabine was investigated by Lübbert et al from Germany on behalf of a multicenter European trial looking at more than 200 patients [11]. These were older patients with AML in whom conventional chemotherapy was not indicated because of factors such as comorbidities, performance status, and poor cytogenetics. Patients received outpatient treatment with a very low dose 3-day regimen (60 mg/m$^2$ total dose per course) for 4 or more courses. Even in the presence of poor-risk cytogenetic characteristics, the drug was well tolerated in the majority of these AML patients who had already been pretreated with higher doses of the drug. The feasibility of the schedule indicated that decitabine may also be useful in maintaining remissions obtained by a standard treatment of AML/MDS.

In regard to recent trials of decitabine, it is interesting to note that various dosing schedules and amounts are used, making determination of optimum dosing difficult at this time. Further complicating the dosing issue is that decitabine, which as a hypomethylating agent increases CD33 expression in AML cells, has been used in combination with gemtuzumab ozogamicin, a CD33 antibody. Interesting preliminary results for the use of this combination in elderly patients with previously untreated AML and high-risk MDS were reported at the ASH 2008 annual meeting by Borthakur et al [12], who are still accruing patients for this study. Questions certainly remain about the use of gemtuzumab in patients who are preparing to undergo transplantation. Also presented at the ASH 2008 annual meeting was an update of a large European trial, a European Organisation for Research and Treatment of Cancer (EORTC) study of low-dose decitabine versus best supportive care in elderly patients with intermediate- or high-risk MDS who were not eligible for intensive chemotherapy. In this study patients were randomized to either low-dose decitabine or supportive care. Patients were balanced in both arms, but the problem was that the difference in overall survival between the 2 groups was not statistically significant.

The conflict of these results with those of the 2 previously mentioned trials is at first glance puzzling. Looked at more closely, however, these conflicting results have several explanations. First, the median number of treatment cycles was only 4 out of a possible 8 with no plan to treat to disease progression. If patients had received additional cycles, there may have been an additional benefit. Additionally, although the number of deaths in each arm were equivalent, the causes of death varied by treatment group. There were more patients who died of disease progression in the supportive care group (18% versus 6%) and more patients who died from toxicity in the decitabine group (16% versus 1%). The higher doses of decitabine used in this study may have contributed to the higher toxicity. Thus, the various trials used different doses of decitabine, and in the latter trial most patients did not receive more than 2 cycles of treatment. Thus, further investigations of the use of decitabine, with and without gemtuzumab, are warranted.

## Conclusions

Approaches to MDS have progressed from considering it a fatal disease that can be addressed only with supportive care to considering it curable with allogeneic transplantation, a procedure that involves complex decisions regarding patient eligibility, transplantation timing, and pretransplantation induction regimens. We are better able to identify patients who are suitable for transplantation, and we can assess possible effects of comorbidity on transplantation outcomes. As reported at the ASH 2008 annual meeting, cardiac disease is the major nonleukemic cause of death posttransplantation.

According to current data, results are fairly equivalent with matched related and matched unrelated donors. More data are needed, however, to determine whether outcomes are better with fully myeloablative versus reduced-intensity transplantation. We have seen in multiple myeloma as well as in MDS that there is decreased transplantation-related mortality with the use of reduced-intensity conditioning prior to transplantation, but in MDS patients the cost is a higher relapse rate. In the past, older patients have not been considered to be good candidates for transplantation, but now we are seeing that many older patients can do well with reduced-intensity transplantation. With all patients who undergo transplantation, graft-versus-host disease remains a major issue.

We are trying to understand the best way to treat patients with hypomethylating agents prior to transplantation. One of the unanswered questions is whether the use of induction with new hypomethylating agents before transplantation will benefit MDS patients. Although a good response may be achieved with these agents, the patient will relapse at some point if treatment is discontinued. So the question in the minds of the referring physicians is whether patients who are responding to hypomethylating agents would derive further benefit from transplantation. Clearly, we're seeing some very interesting results with those patients, but we do not know whether these indications translate into improvements in overall survival. Other concerns are the potential immunomodulatory role of hypomethylating agents for patients going on to allotransplantation and possible mobilization of clonogenic myelodysplastic cells in these patients. These issues remain to be investigated in larger clinical trials.

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# The Hematology Circle: Optimizing Pretransplant Induction Regimens for Multiple Myeloma and Myelodysplastic Syndromes

## CME Assessment Test

1. **Which of the following is true regarding novel-agent induction regimens for multiple myeloma?**
   - A. The use of these regimens has not been shown to affect progression-free survival
   - B. Older regimens such as vincristine, adriamycin, and dexamethasone (VAD) are equally effective
   - C. Patients with high-risk disease usually have poor outcomes with newer agents
   - D. None of the above

2. **What important findings have recently been presented regarding new treatments for multiple myeloma?**
   - A. Complete response to a drug treatment is not a valuable prognostic indicator
   - B. The use of 3-drug regimens is not superior to that of 2-drug regimens
   - C. Mandatory thromboprophylaxis with aspirin is recommended with the use of lenalidomide with dexamethasone
   - D. All of the above

3. **What is the main nonleukemic cause of death in MDS patients?**
   - A. Infection associated with immunosuppression
   - B. Cardiac disease associated with iron overload
   - C. Toxicity associated with chemotherapy
   - D. None of the above

4. **Which of the following are true regarding transplantation outcomes in MDS patients?**
   - A. On the basis of IPSS score, delaying transplantation saves lives in patients with low or intermediate-1 MDS, whereas delaying transplantation risks loss of life in patients with intermediate-2 or high-risk disease
   - B. Patients receiving transplants from matched related donors have much better outcomes than those receiving transplants from matched unrelated donors
   - C. The use of reduced-intensity conditioning is associated with lower relapse rates but higher transplantation-related mortality
   - D. All of the above

## CME Assessment Test Answer Sheet – Program ID #09150

**Release Date: April 30, 2009**
**Last Review Date: April 30, 2009**
**Expiration Date: April 30, 2010**

### 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, 10000 Innovation Drive, Milwaukee, WI 53226. No processing fee is required.**

| | | | | |
|---|---|---|---|---|
| **1.** | A | B | C | D |
| **2.** | A | B | C | D |
| **3.** | A | B | C | D |
| **4.** | A | B | C | D |

## CME Evaluation Form

**Please evaluate the effectiveness of this CME activity on a scale of 1 to 5, with 5 being the highest, by circling your choice. Fax *with the Answer Sheet* to the Office of Continuing and Professional Education, 414-456-6623, or mail to the Office of Continuing Medical Education, Medical College of Wisconsin, 10000 Innovation Drive, Milwaukee, WI 53226.**

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|---|---|
| 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 Maximizing Treatment Outcomes for MDS in the Transplant Patient, published in *Blood and Marrow Transplantation Reviews*, and have answered the CME test questions and completed the Evaluation Form for this activity.

Signature Date

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Specialty Affiliation

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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.*

**Sherman AC, Simonton S, Latif U, Plante TG, Anaissie EJ. Changes in quality-of-life and psychosocial adjustment among multiple myeloma patients treated with high-dose melphalan and autologous stem cell transplantation. *Biol Blood Marrow Transplant*. 2009;15:12-20.**

A growing body of research has evaluated the quality-of-life impact of hematopoietic cell transplantation (HCT). Few studies, however, have focused on patients with multiple myeloma, who frequently receive high-dose therapy followed by autologous HCT. A prospective study evaluated the effects of this treatment regimen on quality of life and psychosocial outcomes in patients with multiple myeloma.

The study included 94 patients undergoing treatment for myeloma: 58 men and 36 women, mean age 55.7 years. Most had stage III disease. At the time of stem cell collection, health-related quality of life was assessed using the Functional Assessment of Cancer Therapy-Bone Marrow Transplant; psychosocial assessments were performed as well. The assessments were repeated after high-dose melphalan therapy and autologous HCT.

Many patients already had physical deficits at the time of stem cell collection, with 70% scoring more than 1 standard deviation below populations norms for physical well-being. Fifty-eight percent scored below norms for functional well-being; 95% had at least moderate fatigue, and 39% had significant pain. About 40% of myeloma patients had clinically significant anxiety, depression, and/or cancer-related distress.

At posttreatment assessment, several outcomes had worsened significantly, including treatment-related concerns, depression, and life satisfaction. There were no significant decrements in pain or social functioning, however. The functional declines after HCT for multiple myeloma were generally less than anticipated.

Few previous studies have provided data on older patients. The new results showed no greater impact of treatment on quality of life in older myeloma patients compared to younger patients. On multivariate analysis, older patients appeared to have better quality of life and less depression at the pretransplantation assessment.

Patients receiving high-dose chemotherapy and HCT for multiple myeloma experience significant disruptions in several areas of health-related quality of life. The decrease in physical functioning after HCT may be less than expected. Screening is needed to identify the substantial number of patients with high distress before and after HCT.

**Chakraborty S, Sun CL, Francisco L, et al. Accelerated telomere shortening precedes development of therapy-related myelodysplasia or acute myelogenous leukemia after autologous transplantation for lymphoma. *J Clin Oncol*. 2009;27:791-798.**

Patients undergoing autologous hematopoietic cell transplantation (HCT) for Hodgkin's or non-Hodgkin's lymphoma are at high risk of therapy-related myelodysplasia or acute myelogenous leukemia (t-MDS/AML). The sequence of cellular and molecular changes leading to this complication is unknown. This study evaluated the possible role of telomere shortening in the development of t-MDS/AML after autologous HCT for Hodgkin's or non-Hodgkin's lymphoma.

Of 287 patients undergoing autologous HCT for Hodgkin's or non-Hodgkin's lymphoma, 9 developed t-MDS/AML and had adequate samples for evaluation. These cases were matched to 24 control patients without t-MDS/AML. Changes in telomere length over time were compared for both groups.

The patients with t-MDS/AML had an initial increase in telomere length from before to 100 days after HCT, followed by accelerated telomere shortening compared to control patients. In a linear mixed effect model, t-MDS/AML was significantly associated with the rate of telomere shortening from day 100 to 3 years in both total cells and myeloid cells. The rate of telomere shortening in total cells was –1.59 per 100 days in t-MDS/AML cases, compared with –2.15 per 100 days in controls. In myeloid cells, the rates were –0.81 versus –0.07 per 100 days, respectively.

These changes were independent of other risk factors for t-MDS/AML. The patients with t-MDS/AML also showed reduced generation of committed progenitor cells, suggesting reduced regenerative capacity of hematopoietic stem cells.

Patients who develop t-MDS/AML after autologous HCT for Hodgkin's or non-Hodgkin's lymphoma have accelerated telomere loss compared to patients without t-MDS/AML. The changes in telomere dynamics may indicate increased clonal proliferation or altered telomere regulation in premalignant cells. Telomere shortening may be an important contributor to leukemic transformation in t-MDS/AML.

**Basara N, Schulze A, Wedding U, et al. Early related or unrelated haematopoietic cell transplantation results in higher overall survival and leukaemia-free survival compared with conventional chemotherapy in high-risk acute myeloid leukaemia patients in first complete remission. *Leukemia*. 2009;23:635-640.**

Allogeneic hematopoietic cell transplantation (HCT) reduces the risk of relapse in patients with acute myeloid leukemia (AML), but also increases treatment-related mortality. Studies using "genetic randomization," based on cytogenetic prognostic profiles, have reported that HCT improves leukemia-free survival in AML patients in first complete remission. This study evaluated the effects of allogeneic HCT on disease-free and overall survival in patients with poor-risk AML.

Data on 708 AML patients enrolled in 2 successive East German Study Group trials identified 138 patients with unfavorable cytogenetic profiles: complex karyotype, del(5q)/–5, del(7q)/–7, abn(3q26), and abn(11q23). Induction chemotherapy produced a first complete remission in 77 patients, who were then eligible for allogeneic HCT. Of these, 47 patients received related or unrelated HCT, and 30 patients received chemotherapy/autologous HCT. Allogeneic HCT was performed after a median of 2 cycles of consolidation chemotherapy in the first trial and 1 cycle in the second trial.

Median follow-up was 19 months. Patients with an HCT donor had significantly better overall survival at 2 years (52%, compared to 24% for patients without a donor). Most of the difference reflected a lower relapse rate in the HCT group (39%, compared to 77% in the chemotherapy group). Treatment-related mortality was 15% and 5%, respectively, and the difference was not significant.

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