

## Recent Advances in the Treatment of MDS

---

A Review of Presentations From  
the 9th International Symposium  
on Myelodysplastic Syndromes  
Florence, Italy  
May 16–19, 2007

With an introduction by:

**Alan F. List, MD**

Professor

H. Lee Moffitt Cancer Center  
& Research Institute



# EDITORIAL ADVISORY BOARD

## Editor-in-Chief

**Bruce D. Cheson, MD**  
Georgetown University Hospital  
Lombardi Cancer Center

## Section Editors

### Oncology

**James L. Abbruzzese, MD**  
The University of Texas  
M. D. Anderson Cancer Center

**Mark J. Ratain, MD**  
The University of Chicago

### Hematologic Malignancies

**Clara D. Bloomfield, MD**  
Ohio State University  
Comprehensive Cancer Center

### Hematology

**Craig M. Kessler, MD**  
Georgetown University  
Medical School  
Lombardi Cancer Center

---

**David B. Agus, MD**  
Cedars-Sinai Medical Center  
University of California,  
Los Angeles

**Kenneth C. Anderson, MD**  
Dana-Farber Cancer Institute

**Bart Barlogie, MD, PhD**  
University of Arkansas  
for Medical Sciences

**Ralph V. Boccia, MD**  
Private practice

**James R. Berenson, MD**  
Institute for Myeloma  
& Bone Cancer Research  
West Hollywood, CA  
**Howard A. Burris III, MD**  
The Sarah Cannon  
Cancer Center

**John Byrd, MD**  
Ohio State University  
Comprehensive Cancer Center

**Mitchell S. Cairo, MD**  
Columbia University

**George P. Canellos, MD**  
Dana-Farber Cancer Institute  
Harvard Medical School

**Michael A. Carducci, MD**  
The Sidney Kimmel  
Comprehensive Cancer Center  
at Johns Hopkins

**Edward Chu, MD**  
Yale Cancer Center,  
Yale University

**Bertrand Coiffier, MD**  
Hopices Civils de Lyon  
Centre Hospitalier Lyon-Sud

**Jeffrey Crawford, MD**  
Duke University Medical Center

**David C. Dale, MD**  
University of Washington

**George D. Demetri, MD**  
Dana-Farber Cancer Institute  
Harvard Medical School

**Brian G. M. Durie, MD**  
Cedars-Sinai Comprehensive  
Cancer Center  
International Myeloma  
Foundation

**Lee M. Ellis, MD**  
The University of Texas  
M. D. Anderson Cancer Center

**Elihu H. Estey, MD**  
The University of Texas  
M. D. Anderson Cancer Center

**David S. Ettinger, MD**  
The Sidney Kimmel  
Comprehensive Cancer Center  
at Johns Hopkins

**James Feusner, MD**  
Children's Hospital Oakland

**Robert A. Figlin, MD**  
City of Hope National  
Medical Center

**Stephen J. Forman, MD**  
City of Hope National  
Medical Center

**Charles Fuchs, MD, MPH**  
Dana-Farber Cancer Institute

**Richard M. Goldberg, MD**  
University of North Carolina  
at Chapel Hill

**Michael S. Gordon, MD**  
Premiere Oncology of Arizona

**William Gradishar, MD**  
Northwestern University

**F. Anthony Greco, MD**  
The Sarah Cannon Cancer Center

**Stephanie A. Gregory, MD**  
Rush University/Rush Medical College  
Rush University Medical Center  
Chicago, IL

**Stuart A. Grossman**  
The Sidney Kimmel  
Comprehensive Cancer Center  
at Johns Hopkins

**John D. Hainsworth, MD**  
The Sarah Cannon Cancer Center

**Roy S. Herbst, MD, PhD**  
The University of Texas  
M. D. Anderson Cancer Center

**Sundar Jagannath, MD**  
St. Vincent's Comprehensive  
Cancer Center

**David H. Johnson, MD**  
Vanderbilt University Medical Center  
Vanderbilt-Ingram Cancer Center

**Brad S. Kahl, MD**  
University of Wisconsin

**Hagop M. Kantarjian, MD**  
The University of Texas  
M. D. Anderson Cancer Center

**Lawrence D. Kaplan, MD**  
University of California,  
San Francisco

**Neil E. Kay, MD**  
Mayo Clinic

**Hedy Lee Kindler, MD**  
University of Chicago

**John M. Kirkwood, MD**  
University of Pittsburgh  
Cancer Institute

**Corey J. Langer, MD**  
Fox Chase Cancer Center  
Temple University  
Medical School

**Richard A. Larson, MD**  
University of Chicago

**John P. Leonard, MD**  
Weill Medical College  
of Cornell University  
New York Presbyterian Hospital

**John S. Macdonald, MD**  
St. Vincent's Comprehensive  
Cancer Center

**Maurie Markman, MD**  
The University of Texas M. D. Anderson  
Cancer Center

**John L. Marshall, MD**  
Georgetown University

**Kathy D. Miller, MD**  
Indiana University School of Medicine

**Ruth O'Regan, MD**  
Winship Cancer Institute  
Emory University

**Thomas L. Ortel, MD, PhD**  
Duke University Medical Center

**Anders Österborg, MD, PhD**  
Karolinska Hospital

**Marshall R. Posner, MD**  
Dana-Farber Cancer Institute  
Harvard Medical School

**Leonard Saltz, MD**  
Memorial Sloan-Kettering  
Cancer Center

**Alan B. Sandler, MD**  
Vanderbilt University Medical Center  
Vanderbilt-Ingram Cancer Center

**Charles A. Schiffer, MD**  
Karmanos Cancer Institute  
Wayne State University  
School of Medicine

**Richard L. Schilsky, MD**  
University of Chicago

**Lee Schwartzberg, MD**  
The West Clinic

**George W. Sledge Jr., MD**  
Indiana University Cancer Center

**Mark A. Socinski, MD**  
Lineberger Comprehensive  
Cancer Center  
University of North Carolina

**Margaret Tempero, MD**  
University of California,  
San Francisco Comprehensive  
Cancer Center

**Joel E. Tepper, MD**  
University of North Carolina  
School of Medicine

**Alan P. Venook, MD**  
University of California,  
San Francisco Comprehensive  
Cancer Center

**Nicholas Vogelzang, MD**  
Nevada Cancer Institute

**Everett E. Vokes, MD**  
University of Chicago

**Peter H. Wiernik, MD**  
New York Medical College  
Our Lady of Mercy Cancer Center

**John R. Wingard, MD**  
University of Florida  
College of Medicine

**Norman Wolmark, MD**  
Drexel University College  
of Medicine

## Table of Contents

Introduction: An Overview of the Current Treatment of Myelodysplastic Syndromes Alan F. List, MD	4
<b>Presentation Summaries:</b>	<b>6</b>
• Value of Transfusion-free Living in MDS: Results of Health Utility Interviews With Patients TF Goss, A Szende, C Schaefer, R Knight, K Heptinstall, M Lübbert, B Deschler, P Fenaux, GL Mufti, S Killickm, AF List	6
• Cost of Transfusion Dependency Among Managed Care Patients With Myelodysplastic Syndromes JR Frytak, HJ Henk, CM de Castro, R Halpern, M Nelson	7
• Cytogenetic Response to Lenalidomide Is Associated With Improved Survival in Patients With MDS and Chromosome 5q Deletion A List, K Wride, G Dewald, J Bennett, A Giagounidis, S Kurtin, R Knight	8
• Cytopenias Correlate With Response to Lenalidomide in Del 5q MDS Patients MA Sekeres, JP Maciejewski, A Giagounidis, K Wride, R Knight, A List	10
• Disease Progression in Del(5q) Myelodysplastic Syndromes Patients Treated With Lenalidomide: Analysis of Risk Factors and Long-term Outcome in 45 Patients AAN Giagounidis, S Haase, V Lohrbacher, M Heinsch, B Schuran, C Aul	11
• Management of Haematological Adverse Events in MDS Patients Treated With Lenalidomide	12
• Management of Non-haematological Adverse Events in MDS Patients Treated With Lenalidomide AAN Giagounidis, M Cazzola, P Fenaux, GJ Mufti, P Muus, U Platzbecker, G Sanz, L Cripe, M Von Lilienfeld-Toal, R Wells	

### Included in Index Medicus/PubMed/Medline

#### Disclaimer

Funding for this Conference Presentations Review has been provided through an educational grant from Celgene Corporation. Support of this monograph does not imply the supporter's agreement with the views expressed herein. Every effort has been made to ensure that drug usage and other information are presented accurately; however, the ultimate responsibility rests with the prescribing physician. Millennium Medical Publishing, Inc., the supporters, and the participants shall not be held responsible for errors or for any consequences arising from the use of information contained herein. Readers are strongly urged to consult any relevant primary literature. No claims or endorsements are made for any drug or compound at present under clinical investigation.

# Introduction

Alan F. List, MD  
Professor of Oncology & Medicine  
Deputy Physician in Chief  
Chief, Malignant Hematology Division  
H. Lee Moffitt Cancer & Research Institute  
Tampa, Florida

The 9th International Symposium on Myelodysplastic Syndromes (MDS), held in Florence, Italy, May 16–19, 2007, featured several key presentations on the management of patients with transfusion-dependent MDS. In this monograph, we highlight six presentations, emphasizing the impact of transfusion dependence on quality of life, the financial burden of transfusion dependency, and new insights into the immunomodulatory drug lenalidomide and its use in patients with deletion 5q MDS.

Most patients with MDS develop transfusion-dependent anemia over the course of their disease, resulting in unrelenting fatigue and decreased quality of life. Until recently the management of patients with MDS, particularly patients with lower risk disease, languished, with a reliance on blood product and growth factor administration. Now, however, new therapeutics are available that can restore effective erythropoiesis and, potentially, alter the natural history of disease. The US Food and Drug Administration (FDA) has approved three agents for the treatment of MDS in the past 3 years: lenalidomide (Revlimid, Celgene), azacitidine (Vidaza, Pharmion), and decitabine (Dacogen, MGI Pharma).

Recent data indicate that transfusion dependence has a greater impact on patient health than was previously recognized. In addition to the threat of serious organ complications caused by iron overload, transfusion dependence adversely affects survival and increases the risk of leukemia transformation. In a retrospective study by investigators at the University of Pavia in Italy, an incremental increase in red blood cell (RBC) transfusion burden among MDS patients with less than 5% bone marrow blasts was associated with a proportional reduction in overall survival and leukemia-free survival.<sup>1,2</sup> This implies that the severity of anemia per se is a key variable limiting the otherwise favorable natural history of patients with lower risk disease. More importantly, recent data from a randomized phase III trial by the Eastern Cooperative Oncology Group (ECOG) that compared treatment with recombinant erythropoietin to best supportive care showed improved overall survival in patients responding to the erythropoiesis-stimulating agents.<sup>3</sup> This has been confirmed by retrospective matching case studies from the

Nordic and French MDS study groups, as well as a significantly reduced potential for leukemia transformation in responding patients.<sup>4,5</sup> These studies provide the first evidence that restoring effective erythropoiesis favorably impacts the natural history of MDS. For those of us who for years viewed the management of lower risk MDS only in terms of symptom control, we now have perhaps a new urgency to consider initiation of erythropoietic promoters that may offer durable clinical benefit.

As hematologists, we appreciate the physiologic benefits of eliminating transfusion dependence in patients with lower risk MDS; however, a systematic evaluation of the value patients place on this outcome has been lacking. Goss and colleagues conducted structured interviews of 47 MDS patients in four counties in order to characterize the impact of transfusion dependence on patient quality of life.<sup>6</sup> The patients surveyed had been diagnosed with MDS for an average of 5 years and most had received RBC transfusions. When asked to compare living with varying levels of transfusion dependence for 5 years or living in perfect health for a shorter period of time, patients strongly preferred transfusion independence over transfusion dependence or a reduced transfusion burden.

Improvements in health outcome or quality of life must be balanced by the cost of the intervention. A randomized phase II study by the French MDS Study Group comparing treatment with erythropoiesis-stimulating agents to best supportive care showed that growth factor management was associated with a higher financial cost.<sup>7</sup> Frytak and coworkers evaluated the economic burden of transfusion management in patients with MDS by analyzing a large managed care claims database for the years 2000–2003 for more than 3,000 patients.<sup>8</sup> The transfusion-dependent MDS cohort had significantly higher adjusted costs relative to the non-transfusion-dependent cohort, with total annual costs estimated at over \$51,000 and \$19,800, respectively ( $P < .001$ ). Costs increased incrementally with rising transfusion frequency.

Lenalidomide was approved by the FDA in December 2005 for the treatment of transfusion-dependent anemia in patients with MDS and chromosome 5q deletion. In the registration trial that secured lenalidomide's approval in the United States, 76% of patients receiving lenalidomide had a 50% or greater reduction in transfusions, with 67% achieving transfusion independence.<sup>9</sup> A companion study (MDS-002) that evaluated transfusion response in low-/intermediate 1-risk patients without deletion 5q highlighted significant differences in response rate and mechanism of action that appear to be karyotype-dependent.<sup>10</sup> A response of transfusion independence in deletion 5q patients strictly correlates with cytogenetic

response, indicating that suppression of the deletion 5q clone is essential for transfusion independence. In patients without deletion 5q, the overall frequency of transfusion independence was lower (26%), with infrequent improvement in cytogenetic abnormalities or cytologic dysplasia, suggesting that in this population lenalidomide directly affects the MDS clone to restore RBC production.

The importance of suppression of the clone in patients with deletion 5q MDS was highlighted in two presentations. Sekeres et al retrospectively analyzed variables associated with response to lenalidomide in the MDS-003 trial.<sup>11</sup> A 50% or greater reduction in platelet count within the first 8 weeks of therapy was associated with a higher probability of achieving RBC transfusion independence ( $P=.005$ ). A second presentation analyzed the potential for clonal suppression, as measured by cytogenetic response, to alter the natural history of disease.<sup>12</sup> The study included patients with deletion 5q from four prospective lenalidomide clinical trials. Among the 168 patients evaluated, cytogenetic response had the highest predictive value for prolonged overall survival in a multivariate analysis (hazard ratio=5.3;  $P<.001$ ). The 10-year survival estimate for cytogenetic responders (partial and complete) was 78% compared to 4% for nonresponders or unevaluable patients. Not surprisingly, cytogenetic response also afforded protection from acute myeloid leukemia (AML) progression, with a 10-year estimate of the risk for leukemia progression of 15% in responding patients compared to 67% in the cytogenetic nonresponding or unevaluable patients ( $P=.010$ ). Despite the retrospective nature of the analysis, the results suggest that lenalidomide may alter the natural history of disease and perhaps extend survival in cytogenetic responders. Giagounidis and coworkers analyzed variables associated with disease progression in 44 patients treated on the MDS-003 trial at their institution in Duisburg, Germany.<sup>13</sup> Patients who progressed to more advanced types of MDS or to AML had unfavorable features prior to lenalidomide treatment, such as elevated bone marrow blasts or complex karyotypes. The MDS-003 study results showed that the lack of a cytogenetic response is independently predictive of disease progression. Collectively, these data support the notion that successful suppression of the deletion 5q clone with lenalidomide decreases leukemia potential in patients with deletion 5q MDS.

The use of lenalidomide in patients with deletion 5q MDS requires balancing the goal of clonal suppression with the potential for ensuing cytopenias. Two presentations highlighted recent consensus panel recommendations for the management of lenalidomide-associated adverse effects.<sup>14,15</sup> Neutropenia and thrombocytopenia, now recognized as likely important surrogate markers of successful suppression of the deletion 5q clone, are the most common complications of lenalidomide treatment. The

panel recommends weekly complete blood counts during the first 2 months of treatment, extending to biweekly thereafter. Coadministration of myeloid growth factors is suggested for patients with absolute neutrophil counts less than 1,000 cells/mm<sup>3</sup>. Patients should report febrile episodes during lenalidomide treatment. Although thrombocytopenia is transient, severe platelet depletion (<25,000 cells/mm<sup>3</sup>) warrants treatment interruption until higher platelet levels are restored. Serious nonhematologic adverse events are relatively infrequent and include pruritus and rash, which can be managed conservatively with antihistamines and emollients. Prospective monitoring for endocrine effects such as hypothyroidism should be done throughout the course of therapy. Although diarrhea may arise as a direct effect of the agent, lactose present in the lenalidomide formulation may exacerbate symptoms and thereby improves with lactase enzyme supplementation. As lenalidomide is structurally related to thalidomide, a potential teratogenic side effect cannot be ruled out.

The presentations discussed herein highlight the importance of transfusion independence in patients with MDS and, more importantly, describe the potential benefits of lenalidomide beyond the treatment of transfusion-dependent anemia.

## References

1. Malcovati L, Giovanni M, Pascutto C, et al. Prognostic factors and life expectancy in myelodysplastic syndromes classified according to WHO criteria: a basis for clinical decision making. *J Clin Oncol*. 2005;23:7594-7603.
2. Malcovati L, Giovanni M, Cazzola M. Predicting survival and leukemic evolution in patients with myelodysplastic syndrome. *Haematologica*. 2006;91:1588-1590.
3. Miller K, Haesook K, Greenberg P, et al. Phase III prospective randomized trial of EPO with or without G-CSF versus supportive therapy alone in the treatment of myelodysplastic syndromes (MDS): results of the ECOG-CLSG Trial (E1996). *Blood*. 2004;104:70.
4. Jadersten M, Malcovati L, Dybedal I, et al. Treatment with erythropoietin and G-CSF improves survival in MDS patients with low transfusion need. *Blood*. 2006;108:521a.
5. Park S, Grabar S, Kelaidi C, et al; for the Groupe Francophone des myelodysplasies (GFM). Has treatment with EPO +/- G-CSF an impact on progression to AML and survival in low/int-1-risk MDS? A comparison between French-EPO patients and the IMRAW database. *Leuk Res*. 2007;31(suppl 1):S113.
6. Goss TF, Szende A, Schaefer C, et al. Value of transfusion-free living in MDS: results of health utility interviews with patients. *Leuk Res*. 2007; 31(suppl 1):S156.
7. Casadevall N, Dubois S, Hemery F, et al. Health, economic, and quality-of-life effects of erythropoietin and granulocyte colony-stimulating factor for the treatment of myelodysplastic syndromes: a randomized, controlled trial. *Blood*. 2004;104:321-327.
8. Frytak JR, Henk HJ, de Castro CM, Halpern R, Nelson M. Cost of transfusion dependency among patients with myelodysplastic syndromes. *Leuk Res*. 2007;31(suppl 1):S156.
9. List A, Dewald G, Bennett J, et al. Lenalidomide in the myelodysplastic syndrome with chromosome 5q deletion. *N Engl J Med*. 2006;355:1456-1465.
10. List AF, Dewald G, Bennett J, et al. Results of the MDS-002 and -003 international phase II studies evaluating lenalidomide in the treatment of transfusion-dependent patients with myelodysplastic syndrome. *Haematologica*. 2005;90(suppl 2):307a.
11. Sekeres M, Maciejewski JP, Giagounidis A, Wride K, Knight R, List A. Cytopenias correlate with response to lenalidomide in del 5q MDS patients. *Leuk Res*. 2007;31(suppl 1):S37-S38.
12. List A, Wride K, Dewald G, et al. Cytogenetic response to lenalidomide is associated with improved survival in patients with chromosome 5q deletion. *Leuk Res*. 2007;31(suppl 1):S38.
13. Giagounidis AAN, Haase S, Lohrbacher V, Heinsch M, Schuran B, Aul C. Disease progression in del(5q) MDS patients treated with lenalidomide: analysis of risk factors and long-term outcome in 45 patients. *Leuk Res*. 2007;31(suppl 1):S156.
14. Giagounidis AAN, Cazzola M, Fenaux P, et al. Management of non-hematological adverse events in MDS patients treated with lenalidomide. *Leuk Res*. 2007;31(suppl 1):S156.
15. Giagounidis AAN, Cazzola M, Fenaux P, et al. Management of hematological adverse events in MDS patients treated with lenalidomide. *Leuk Res* 2007;31(suppl 1):S156.

# Recent Advances in the Treatment of MDS

A Review of Presentations From  
the 9th International Symposium  
on Myelodysplastic Syndromes  
Florence, Italy  
May 16–19, 2007

## Value of Transfusion-free Living in MDS: Results of Health Utility Interviews With Patients

TF Goss, A Szende, C Schaefer, R Knight,  
K Heptinstall, M Lübbert, B Deschler, P Fenaux,  
GL Mufti, S Killickm, AF List

The majority of patients with myelodysplastic syndromes (MDS) develop clinically significant anemia due to insufficient red blood cell (RBC) production, resulting in the need for RBC transfusions. Due to the negative impact that transfusion dependence has on patient quality of life, a major goal of MDS therapy is to enable transfusion-dependent individuals to achieve transfusion independence. To gauge the value of transfusion-free living among patients with MDS, Goss and colleagues conducted face-to-face interviews with individuals with MDS living in the United States, the United Kingdom, Germany, and France.<sup>1</sup>

The relative value these individuals placed on transfusion independence, a reduced transfusion burden, and transfusion dependence was assessed by examining several quality-of-life domains (eg, fatigue and tiredness, interference with social and family life) using two methods, the feeling thermometer visual analog scale (VAS) and the time-trade-off (TTO) method. The TTO method asked patients to compare living with varying levels of transfusion dependence for 5 years or living in perfect health for a shorter period of time. The VAS ranged from 0 to 100 and the TTO scale ranged from 0 (dead) to 1 (perfect health).

A total of 47 individuals were interviewed for the study. Their mean age was 67 years (range: 29–83 years), and 55% were female. These patients had been diagnosed with MDS a mean of 5 years earlier (range: 1–23 years). The great majority (87%) had received a blood transfusion since their diagnosis, and nearly half (49%) had received a transfusion within the past 3 months. In a background questionnaire, 45%, 40%, 47%, and 34% of participants reported at least some problems with mobility, usual activities, pain/discomfort, and anxiety/depression, respectively, versus 29%, 25%, 46%, and 28%, respectively, in an age-matched group from the general population.<sup>2</sup> These findings reflect the reduced quality of life faced by individuals with MDS, which may be exacerbated by the need for frequent RBC transfusions.

Not surprisingly, patients preferred transfusion independence much more so than the other two health states in which some level of transfusion is required. Paired *t* tests of the VAS scores showed that individuals with MDS significantly favored transfusion independence over a reduced transfusion burden (78 vs 56;  $P < .001$ ) and transfusion dependence (78 vs 31;  $P < .001$ ). Similar findings were observed with the TTO method, with transfusion independence strongly preferred over a reduced transfusion requirement (0.84 vs 0.77;  $P = .06$ ) and transfusion dependence (0.84 vs 0.60;  $P < .001$ ). The investigators noted that three individuals regarded transfusion dependence as worse than being dead according to the TTO method. Scores on the VAS and TTO scales were similar across all countries.

As the findings illustrate, patients with MDS place a high value on achieving transfusion independence. As such, the investigators stated that future MDS treatments should aim to free patients from the burden of requiring regular RBC transfusions.

**Table 1.** Baseline Characteristics of Transfusion-dependent and Transfusion-independent Individuals With MDS

Characteristic	Transfusion-independent (N=2,864)	Transfusion-dependent (N=336)	P Value
Mean age, years (SD)	69.8 (9.2)	73.6 (9.7)	<.001
Male, n (%)	1,337 (46.7)	189 (56.3)	.001
Type of health plan, n (%)			<.001
• Commercial	1,760 (61.5)	160 (47.6)	
• Medicare	1,039 (36.3)	170 (50.6)	
• Medicaid	65 (2.3)	6 (1.8)	
Region, n (%)			<.001
• Northeast	538 (18.8)	41 (12.2)	
• Midwest	942 (32.9)	163 (48.5)	
• South	1,171 (40.9)	119 (35.4)	
• West	213 (7.4)	13 (3.9)	
Newly diagnosed MDS, n (%)	275 (9.6)	90 (26.8)	<.001
Renal failure, n (%)	381 (13.3)	54 (16.1)	.161

## Cost of Transfusion Dependency Among Managed Care Patients With Myelodysplastic Syndromes

JR Frytak, HJ Henk, CM de Castro, R Halpern, M Nelson

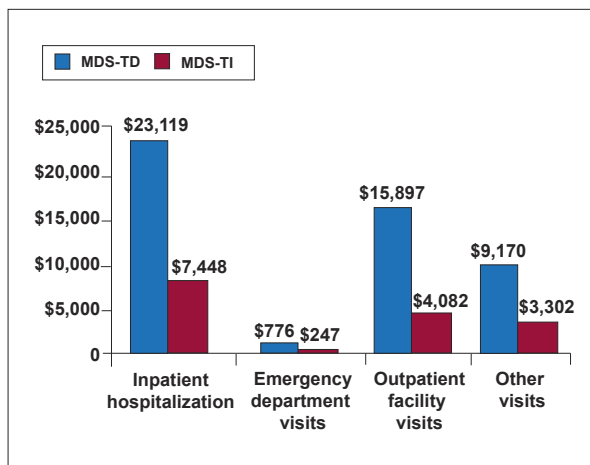
Freedom from transfusion dependence not only offers patients with MDS the prospect of improved quality of life, it also has the potential to dramatically decrease the economic and clinical burden associated with regular RBC transfusions. A retrospective cohort study conducted by Frytak and coworkers sought to estimate the additional cost associated with transfusion dependence among patients with MDS.<sup>3</sup>

Claims information from a large US health plan covering approximately 14 million individuals annually was used to obtain longitudinal patient data. Data for patients with MDS who were at least 55 years of age, received treatment between May 2000 and September 2003, and had at least 6 months of continuous follow-up information were included in the analysis. Patients with chemotherapy-induced anemia were excluded from the analysis. Transfusion dependence was defined as the

need for two or more transfusions within 8 weeks and at least 7 days apart, and the need for a third transfusion within 3–6 months after the first transfusion. Patients were considered to be transfusion-independent if they did not meet these criteria. Demographics, baseline health status, and annualized health care costs were then compared between the transfusion-dependent and -independent groups.

The 336 transfusion-dependent individuals included in the analysis differed significantly from the 2,864 transfusion-independent patients according to several characteristics (Table 1). They were significantly more likely to be older, male, on Medicare, living in the Midwest, and newly diagnosed with MDS. The only characteristic for which the groups did not differ was the proportion with renal failure.

The investigators determined that transfusion-dependent individuals tallied \$31,255 more in medical costs per year than transfusion-independent individuals (\$51,066 vs \$19,811). These additional charges were primarily attributable to greater needs for inpatient hospitalization (2.19 vs 0.6 visits/year), outpatient facility visits (28.4 vs 7.78 visits/year), and office visits (36.34 vs 22.85 visits/year; Figure 1). The difference in pharmacy costs between the transfusion-dependent and -independent groups was relatively small (\$4,457 vs \$2,926).



**Figure 1.** Unadjusted annualized mean medical cost for myelodysplastic syndromes (MDS) cohorts.

TD = transfusion-dependent; TI = transfusion-independent.

This study clearly illustrates the high economic burden of MDS for any diagnosed patient, but the particularly onerous burden for those who are transfusion-dependent is apparent. Clinicians treating patients with MDS should bear in mind that this economic burden of transfusion dependence can affect patient quality of life just as dramatically as does the physical burden.

## Cytogenetic Response to Lenalidomide Is Associated With Improved Survival in Patients With MDS and Chromosome 5q Deletion

A List, K Wride, G Dewald, J Bennett,  
A Giagounidis, S Kurtin, R Knight

Lenalidomide is a novel immunomodulatory drug with proven ability to reduce transfusion requirements and reverse cytologic and cytogenetic abnormalities in patients with MDS. The erythropoietic activity produced by lenalidomide is karyotype-dependent, with disparate but complementary mechanisms of action.<sup>4</sup> For example, the transfusion response in patients with deletion of

chromosome 5q (del[5q]) correlates with clonal suppression and increased medullary apoptosis. In contrast, in patients with MDS lacking the del(5q) abnormality, lenalidomide promotes erythropoiesis in the dysplastic clone, thereby producing a reduction in apoptosis and the proliferation index.

To evaluate the potential long-term benefit of clonal suppression produced by lenalidomide in patients with MDS characterized by the del(5q) abnormality, List and colleagues analyzed the results from four prospective clinical trials of lenalidomide in the del(5q) patient population.<sup>5</sup> A total of 168 patients from the MDS-001 (n=12), MDS-002 (n=1), MDS-003 (n=148), and MDS-PK-002 (n=7) studies were included in the analysis. Most of the patients (88%) included in the current study were enrolled in the multicenter, phase II MDS-003 trial in which they received lenalidomide 10 mg/day. A subset of patients in the MDS-001 study received lenalidomide 25 mg/day.

The clinical endpoints assessed by List et al included the duration of RBC transfusion independence, overall survival, and acute myeloid leukemia (AML) evolution. Transfusion independence was defined as a period of at least 8 consecutive weeks during which no transfusions were given and the hemoglobin concentration rose by at least 1 g/dL. Variables included in multivariate analyses of these endpoints were age, sex, Eastern Cooperative Oncology Group (ECOG) performance status, French-American-British (FAB) subtype, International Prognostic Scoring System (IPSS) category, karyotype complexity, the presence of 5q- syndrome, the need for RBC transfusions, thrombocytopenia, marrow blast percentage, time to response, and disease duration.

Patients had a median age of 71 years (range: 37–95 years) and 65% were female. The patients had been living with MDS for a median of 2.5 years (range: 0.1–20.7 years). As expected, the individuals were generally heavily transfused: Patients required a median of 5 RBC units every 8 weeks, and 81% required at least 2 packed RBC units every 4 weeks. Assessment of cytogenetic features at baseline revealed that 76% had the del(5q) abnormality in isolation, 16% had del(5q) plus one additional cytogenetic lesion, and 7% had a complex cytogenetic pattern consisting of three or more chromosomal abnormalities. Of those with the just the del(5q) abnormality, 29% had the 5q- syndrome.

The overall transfusion response rate was impressive at 76%, with 67% of patients achieving transfusion independence and an additional 8% attaining at least a 50% reduction in the number of needed transfusions. Moreover, the time to transfusion independence was brisk, occurring within a median of 4.7 weeks (range: 1–49 weeks). There was no significant difference in

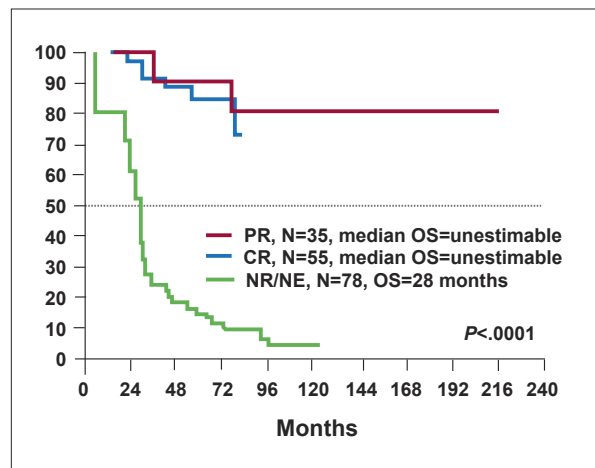
**Table 2.** Predictors of a Longer Duration of Treatment Independence and Longer Overall Survival According to Multivariate Analysis

Prognostic Variable	Hazard Ratio	P Value
<b>For longer duration of treatment independence</b>		
• 5q- syndrome	4.972	<.001
• RBC transfusions <4 units every 8 weeks	3.081	.002
• Low-risk IPSS	3.060	.003
• Age ≤70 years	2.397	.007
• Lower ECOG PS	2.024	.026
<b>For longer survival</b>		
• Cytogenetic response	5.295	<.001
• Age ≤70 years	2.689	.033
• RBC transfusions <4 units every 8 weeks	3.521	.037
• Platelets <100,000 cells/mm <sup>3</sup>	2.536	.072

ECOG PS=Eastern Cooperative Oncology Group performance status; IPSS=International Prognostic Scoring System; RBC=red blood cells.

the transfusion response rate by cytogenetic pattern. The overall frequency of transfusion independence was comparable at 73% for patients with the del(5q) abnormality in isolation, 52% for those with del(5q) plus one additional abnormality, and 67% for those with a complex karyotype. As of May 7, 2007, the median duration of RBC transfusion independence was 2.2 years (range: 0.2–4.8+ years); exactly 65% of individuals had been transfusion-independent for at least 1 year, and 42% had been transfusion-independent for at least 2 years.

Of 131 patients with at least 20 postbaseline metaphases available for analysis, 69% achieved a cytogenetic response (42% complete response, 27% partial response). As with the transfusion response, no significant difference in response rate was observed according to cytogenetic pattern. The overall complete cytogenetic response rate was nearly identical between groups: 42% for patients with the del(5q) abnormality in isolation, 42% for those with del(5q) plus one additional abnormality, and 43% for those with a complex karyotype. Multivariate analysis revealed that the presence of 5q- syndrome was the strongest predictor of a longer duration of transfusion independence and cytogenetic response was the strongest predictor of longer overall survival (Table 2).



**Figure 2.** Overall survival from myelodysplastic syndromes diagnosis according to cytogenetic response.

CR=complete cytogenetic response; NE=not evaluable; NR=no cytogenetic response; OS = overall survival; PR=partial cytogenetic response.

Kaplan-Meier survival curves corroborated the multivariate findings by showing that patients who attained a complete or partial cytogenetic response with lenalidomide had not yet reached the median estimable survival time, whereas the estimated overall survival duration for nonevaluable patients or those with no cytogenetic response was 28 months ( $P<.0001$ ; Figure 2). At 10 years, the estimated survival for those with a cytogenetic response was at least 75% compared with 4% for those with no cytogenetic response.

In conjunction with overall survival, AML evolution also significantly correlated with a cytogenetic response. After 10 years, the cumulative risk of AML evolution was 15% for patients with a complete or partial cytogenetic response compared with a rate of 67% for nonevaluable or nonresponding patients. In this latter group, the mean time to AML development was 66.7 months.

Based on these findings, List concluded by stating that lenalidomide yields high erythroid and cytogenetic response rates and enables prolonged periods of transfusion independence in lower-risk, transfusion-dependent individuals with del(5q) MDS. Achieving a cytogenetic response appears to be a critical determinant for long-term survival and for suppressing the risk for disease progression. As such, optimizing the cytogenetic response, particularly among patients with high-risk MDS, may help maximize the ability of lenalidomide to modify the course of del(5q) MDS.

**Table 3.** Rate of Transfusion Independence Based on the Development of Treatment-related Cytopenias

Group	n	Rate of Transfusion Independence, %		P Value
		Treatment-related Cytopenia	No Treatment-related Cytopenia	
All patients	147	80	60	.012
• No baseline cytopenia	63	85	59	.024
• Baseline cytopenia	84	71	60	.024
Thrombocytopenia				
• No baseline thrombocytopenia	88	76	47	.005
• Baseline thrombocytopenia	59	67	38	.005
Neutropenia				
• No baseline neutropenia	88	82	56	.018
• Baseline neutropenia	59	58	64	.75

## Cytopenias Correlate With Response to Lenalidomide in Del 5q MDS Patients

MA Sekeres, JP Maciejewski, A Giagounidis, K Wride, R Knight, A List

Lenalidomide targets malignant cells in the bone marrow microenvironment by abrogating the effects of cytokines and directly causing cytotoxicity. This mechanism of action may cause the transient thrombocytopenia and neutropenia that is commonly seen during the initial period of lenalidomide treatment. Sekeres and colleagues conducted a retrospective analysis of data from the phase II MDS-003 trial to determine if the occurrence of thrombocytopenia and/or neutropenia correlates with the response to lenalidomide therapy.<sup>6</sup>

MDS-003 was designed to assess the efficacy of lenalidomide in low-risk, transfusion-dependent patients with del(5q) MDS. A total of 148 patients were randomly assigned to receive 10 mg of lenalidomide for 21 days every 4 weeks or daily; hematologic, bone marrow, and cytogenetic changes were assessed after 24 weeks of treatment.

The results from MDS-003 have previously been published.<sup>7</sup> The median age of participants was 71 years (range: 37–95 years), and they had been diagnosed with MDS for a median of 2.5 years (range: 0.1–20.7 years). The majority (81%) had low- or intermediate 1–risk MDS; 5% had intermediate 2– or high-risk MDS and

the IPSS score for the remaining 14% was unclassified. Consistent with the data previously presented by Dr. List,<sup>5</sup> 76% of patients in MDS-003 attained a transfusion response, of which 67% achieved complete transfusion independence. Similarly, 73% achieved a cytogenetic response, of which 45% attained a complete cytogenetic response.

Dr. Sekeres noted that at baseline 40% of patients had neutropenia (absolute neutrophil count [ANC] <2,000 cells/mm<sup>3</sup>), 40% had thrombocytopenia (platelet count <150,000 cells/mm<sup>3</sup>), and 57% had either neutropenia or thrombocytopenia. During lenalidomide therapy, the MDS-003 investigators reported that 55% of patients developed grade 3/4 neutropenia, defined as an ANC less than 1,000 cells/mm<sup>3</sup>, and 44% developed grade 3/4 thrombocytopenia, defined as a platelet count below 50,000 cells/mm<sup>3</sup> (to account for patients who presented with cytopenias, the definitions used for treatment-related neutropenia and thrombocytopenia were functional rather than absolute). Largely because of these cytopenias, 84% of patients required lenalidomide dose reduction during the study.

The development of treatment-related cytopenias was assessed within the first 8 weeks of therapy. For the current analysis, lenalidomide-related cytopenias were defined slightly differently from the definitions used during the MDS-003 trial to better reflect functional status. Treatment-related neutropenia was defined as a drop in ANC of 75% or more, and treatment-related thrombocytopenia was defined as a drop in platelet count of 50% or more. In conjunction, the response to lenalidomide was assessed using the 2000 MDS International Working Group criteria.<sup>8</sup>

Overall, 80% of patients who developed treatment-related thrombocytopenia or neutropenia achieved transfusion independence versus 60% of patients who did not meet the criteria for these cytopenias ( $P=.012$ ). Significantly higher rates of transfusion independence were observed irrespective of whether patients had cytopenia at baseline (Table 3).

Patients who developed thrombocytopenia during lenalidomide treatment were significantly more likely to achieve transfusion independence than patients who did not develop thrombocytopenia, regardless of whether they had baseline thrombocytopenia. Patients who were nonneutropenic at baseline and developed neutropenia during treatment demonstrated significantly higher rates of transfusion independence compared with those who did not develop treatment-related neutropenia; however, among patients who were neutropenic at baseline, there was no significant difference in response rate among those who did and did not develop neutropenia during treatment.

When the investigators conducted a multivariate analysis with baseline and on-treatment variables, they found that the development of thrombocytopenia or neutropenia during lenalidomide therapy independently and significantly correlated with a transfusion response. Patients who developed at least a 75% drop in ANC during treatment had 2.680-fold higher odds of achieving transfusion independence than those who showed lesser drops ( $P=.04$ ). Likewise, individuals who had at least a 50% decrease in platelet count were 2.794 times more likely to achieve transfusion independence than those with smaller decreases ( $P=.05$ ).

When another multivariate analysis was conducted to identify factors associated with the duration of transfusion independence, the development of treatment-related thrombocytopenia fell out of the analysis. The development of neutropenia during therapy demonstrated a trend toward prolonged transfusion independence (hazard ratio: 2.037;  $P=.06$ ) but was just shy of being statistically significant.

These results suggest that the development of thrombocytopenia and/or neutropenia during lenalidomide treatment may reflect the therapeutic effect of lenalidomide on the del(5q) clone. Dr. Sekeres noted that if cytopenias are indeed a marker of lenalidomide activity, additional research would be needed to identify how to best manage these side effects. For example, it will be important to determine if cytopenias are best managed with dose reductions, short-term treatment interruptions, or the addition of growth factor support to full-dose lenalidomide.

## Disease Progression in Del(5q) Myelodysplastic Syndromes Patients Treated With Lenalidomide: Analysis of Risk Factors and Long-term Outcome in 45 Patients

AAN Giagounidis, S Haase, V Lohrbacher, M Heinsch, B Schuran, C Aul

As previously discussed, the results from the MDS-003 trial clearly established the efficacy of lenalidomide in patients with transfusion-dependent MDS with the del(5q) chromosomal abnormality.<sup>7</sup> Some patients, however, experienced disease progression to higher FAB subtypes ( $n=8$ ) or to AML ( $n=8$ ) within the first year of the study, leading to speculation as to whether lenalidomide might promote disease progression in a subset of individuals.

To address this issue, Giagounidis and colleagues performed a retrospective analysis of 45 lenalidomide-treated patients with del(5q) MDS to identify risk factors associated with disease progression.<sup>9</sup> The analysis included 27 women and 18 men with a median age of 71.6 years (range: 34–92 years). All patients initially received oral lenalidomide at a dose of 10 mg/day. Additional therapies included granulocyte colony-stimulating factor (G-CSF) for severe neutropenia (ie, grade >2) and antibiotics. Therapy was interrupted and continued at a lower dose in the event of grade 3 or 4 adverse events.

During the median follow-up time of 25 months (range: 2–41 months), 13 of the 45 patients (28.9%) experienced disease progression, which was defined as an increase in bone marrow blast count leading to a higher FAB classification. The investigators grouped patients according to their bone marrow blast count and cytogenetic profile at baseline to identify any putative risk factors for progression (Table 4). Very few patients (11%) with low-risk status (ie, <5% bone marrow blasts and del[5q] abnormality in isolation) progressed to higher FAB subtypes or AML, in keeping with prior data.<sup>10</sup> Patients with fewer than 5% bone marrow blasts but with the extra risk factor of additional chromosomal abnormalities had a rate of progression (33%) that was slightly higher than previous reports.<sup>11</sup> Roughly half of all patients (47%) with a bone marrow blast count of 5% or more progressed during lenalidomide treatment, consistent with the short expected survival for this patient subgroup.<sup>11</sup> Four out of 6 individuals (66%) with complex karyotypes and high

**Table 4.** Disease Progression Rates According to Baseline Bone Marrow Blast Count and Cytogenetic Profile

Myelodysplastic Syndromes Group	Total Patients, n	Disease Progression, n (%)	No Disease Progression, n (%)
Bone marrow blasts <5%			
• Isolated del(5q)	18	2 (11)	16 (89)
• Del(5q) + additional abnormalities	9	3 (33)	6 (66)
Bone marrow blasts ≥5%			
• Isolated del(5q)	12	4 (33)	8 (66)
• Del(5q) + additional abnormalities	3	3 (100)	0 (0)
Hypocellular	3	1 (33)	2 (66)

bone marrow blast counts progressed during treatment, in accord with the poor prognosis for such patients.<sup>12</sup>

In general, the disease progression rates observed among lenalidomide-treated patients were consistent with the natural transformation rates previously reported. Based on these findings, the investigators concluded that lenalidomide does not lead to excess AML transformation when used by individuals with del(5q) MDS.

## Management of Haematological Adverse Events in MDS Patients Treated With Lenalidomide

## Management of Non-haematological Adverse Events in MDS Patients Treated With Lenalidomide

AAN Giagounidis, M Cazzola, P Fenaux, GJ Mufti, P Muus, U Platzbecker, G Sanz, L Cripe, M Von Lilienfeld-Toal, R Wells

Lenalidomide has recently been approved by the United States Food and Drug Administration for the treatment of patients with transfusion-dependent, low- or intermediate 1-risk MDS with the del(5q) chromosomal abnormality. Although the agent is highly effective at reducing transfusion requirements and reversing cytogenetic abnormalities in this patient population, treatment can be compromised by lenalidomide-related hematologic

**Table 5.** Grade 3/4 Adverse Events Associated With Lenalidomide Treatment in the MDS-003 Trial

Adverse Event	Incidence, %
<b>Hematologic</b>	
• Neutropenia	55
• Thrombocytopenia	44
• Anemia	7
• Leukopenia	6
• Febrile neutropenia	1
• Venous thromboembolism	3
<b>Nonhematologic</b>	
• Rash	6
• Pruritus	3
• Fatigue	3
• Diarrhea	3
• Nausea	3
• Muscle cramps	2

adverse events that necessitate treatment discontinuation or dose reduction.<sup>7</sup> Nonhematologic events can also occur but are less common.

In January 2007, an international group of MDS experts convened to formulate a set of practical guidelines for managing adverse events that develop during lenalidomide treatment. Giagounidis and colleagues presented the group's recommendations in two separate posters at the International Symposium on MDS.<sup>13,14</sup>

**Table 6.** Recommendations for the Management of Hematologic Adverse Events Associated With Lenalidomide

Hematologic Adverse Event	Recommendation
Neutropenia	<ul style="list-style-type: none"> <li>• If ANC &lt;1,000 cells/mm<sup>3</sup>, administer G-CSF or temporarily discontinue lenalidomide to prevent severe neutropenia</li> <li>• If ANC &lt;500 cells/mm<sup>3</sup>, interrupt lenalidomide</li> <li>• Lenalidomide can be reintroduced after ≥1 week of discontinuation provided that ANC ≥750 cells/mm<sup>3</sup></li> </ul>
Febrile neutropenia	<ul style="list-style-type: none"> <li>• Educate patients about the signs and symptoms of febrile neutropenia and how they should respond</li> <li>• Offer specialized hematologic care at all times</li> <li>• Administer broad-spectrum antibiotics within 3 hours of fever onset</li> </ul>
Thrombocytopenia	<ul style="list-style-type: none"> <li>• If platelet count &lt;25,000 cells/mm<sup>3</sup> without platelet support, interrupt lenalidomide</li> <li>• The presence of thrombocytopenia at baseline does not contraindicate lenalidomide use; prophylactic thrombocyte transfusions may be considered until counts rise</li> <li>• Lenalidomide can be introduced after ≥1 week of discontinuation provided that platelet count ≥50,000 cells/mm<sup>3</sup></li> </ul>
VTE	<ul style="list-style-type: none"> <li>• VTE prophylaxis is generally not recommended for patients with MDS</li> <li>• Concomitant use of lenalidomide and erythropoietin is not recommended due to an increased risk for VTE</li> <li>• Inform patients about the risk for VTE and monitor for symptoms</li> <li>• If VTE occurs, interrupt lenalidomide, treat the VTE, and carefully reintroduce lenalidomide once stable anticoagulation has been achieved</li> </ul>
Polycythemia	<ul style="list-style-type: none"> <li>• Depending on ferritin levels, continue lenalidomide and consider a phlebotomy</li> <li>• Polycythemia is usually transient, but treatment interruption may sometimes be necessary</li> </ul>

ANC=absolute neutrophil count; G-CSF=granulocyte colony-stimulating factor; VTE=venous thromboembolism.

During the moderated roundtable discussion, the MDS specialists relied on the results from the MDS-003 trial.<sup>7</sup> They noted that hematologic adverse events occurred frequently and were the most common reason for dose adjustment (Table 5). Transient thrombocytopenia and neutropenia should be expected in most patients early during the treatment course, as these events are associated with a response to therapy.<sup>6</sup> Based on these observations, the group recommended that patients undergo a full blood work-up on a weekly basis during the first 2 months of treatment at a minimum, and possibly up through 5 months of treatment. Biweekly or monthly monitoring may be considered thereafter depending on the blood count results.

To facilitate safe administration of lenalidomide and avoid unnecessary dose reduction or discontinuation that may compromise treatment efficacy, the group defined optimal management protocols for specific hematologic adverse events (Table 6). Supplemental treatment with G-CSF should be considered for patients with an ANC less than 1,000 cells/mm<sup>3</sup> in order to prevent severe neutropenia. Although thrombocytopenia is transient, severe platelet depletion (<25,000 cells/mm<sup>3</sup>) warrants

treatment interruption until higher platelet levels are restored. The panel advises clinicians to provide patients with clear instructions on how to react should febrile neutropenia occur, given that lenalidomide-associated neutropenic sepsis can lead to death. Severe venous thromboembolism (VTE) is a relatively rare (3%) but serious threat during lenalidomide treatment; the panel does not endorse VTE prophylaxis for MDS patients but stressed that concurrent use of lenalidomide and erythropoietin can increase the risk for VTE.

Nonhematologic adverse events occur much less frequently with lenalidomide treatment than hematologic adverse events, and the investigators noted that lenalidomide is generally well tolerated by patients with low- or intermediate 1–risk MDS with del(5q). In MDS-003, the most common nonhematologic adverse events of all grades included pruritus (42%), rash (36%), and dry skin (14%).<sup>7</sup> The incidence of severe nonhematologic events ranged from 2% to 6%, with rash being the most common event of at least grade 3 in severity (Table 5). Unlike thalidomide, lenalidomide, is not associated with dose-dependent peripheral neuropathy, somnolence, or constipation.<sup>15</sup>

**Table 7.** Recommendations for the Management of Nonhematologic Adverse Events Associated With Lenalidomide

Nonhematologic Adverse Event	Recommendation
Rash	<ul style="list-style-type: none"> <li>• No lenalidomide interruption is generally needed, as rash usually resolves within 2–3 weeks</li> <li>• If required, administer supplemental unselective antihistamines (eg, clemastin), topical steroids, or a short course (14 days) of oral prednisone 10 mg/day</li> <li>• If rash is severe, interrupt lenalidomide until rash resolves. In the experience of the panel, lenalidomide can subsequently be restarted without risk of recurrence</li> </ul>
Diarrhea	<ul style="list-style-type: none"> <li>• Treat symptomatically after excluding other underlying causes (eg, anemia, autoimmune disorders)</li> </ul>
Hypothyroidism	<ul style="list-style-type: none"> <li>• Screen for thyroid-stimulating hormone, triiodothyronine (T3), and thyroxine (T4), and monitor during treatment</li> <li>• Thyroid replacement therapy may be needed in the event of hypothyroidism</li> </ul>
Other nonhematologic adverse events	<ul style="list-style-type: none"> <li>• Treat symptomatically after excluding other underlying causes (eg, anemia, autoimmune disorders)</li> </ul>

The expert panel concluded that most of the non-hematologic adverse events that may arise during lenalidomide treatment could be managed without the need for treatment discontinuation. According to their recommendations (Table 7), only severe rash may warrant temporary treatment interruption. In such cases, lenalidomide can be restarted after the rash resolves without risk of recurrence.

## References

- Goss TF, Szende A, Schaefer C, et al. Value of transfusion-free living in MDS: results of health utility interviews with patients. Presented at the 9th International Symposium on Myelodysplastic Syndromes; May 16-19, 2007; Florence, Italy. Abstract P122.
- Kind P, Dolan P, Gudex C, Williams A. Variations in population health status: results from a United Kingdom national questionnaire survey. *BMJ*. 1998;316:736-741.
- Frytak JR, Henk HJ, de Castro CM, Halpern R, Nelson M. Cost of transfusion dependency among managed care patients with myelodysplastic syndromes. Presented at the 9th International Symposium on Myelodysplastic Syndromes; May 16-19, 2007; Florence, Italy. Abstract P132.
- List AF, Baker AF, Green S, Bellamy W. Lenalidomide: targeted anemia therapy for myelodysplastic syndromes. *Cancer Control*. 2006;13(suppl):4-11.
- List A, Wride K, Dewald G, et al. Cytogenetic response to lenalidomide is associated with improved survival in patients with MDS and chromosome 5q deletion. Presented at the 9th International Symposium on Myelodysplastic Syndromes; May 16-19, 2007; Florence, Italy. Abstract C028.
- Sekeres MA, Maciejewski JP, Giagounidis A, Wride K, Knight R, List A. Cytopenias correlated with response to lenalidomide in del 5q MDS patients. Presented at the 9th International Symposium on Myelodysplastic Syndromes; May 16-19, 2007; Florence, Italy. Abstract C027.
- List A, Dewald G, Bennett J, et al. Lenalidomide in the myelodysplastic syndrome with chromosome 5q deletion. *N Engl J Med*. 2006;355:1456-1465.
- Cheson BD, Bennett JM, Kantarjian H, et al. Report of an international working group to standardize response criteria for myelodysplastic syndromes. *Blood*. 2000;96:3671-3674.
- Giagounidis AAN, Haase S, Lohrbacher V, Heinsch M, Schuran B, Aul C. Disease progression in del(5q) myelodysplastic syndromes patients treated with lenalidomide: analysis of risk factors and long-term outcome in 45 patients. Presented at the 9th International Symposium on Myelodysplastic Syndromes; May 16-19, 2007; Florence, Italy. Abstract P146.
- Giagounidis AA, Germing U, Haase S, et al. Clinical, morphological, cytogenetic, and prognostic features of patients with myelodysplastic syndromes and del(5q) including band q31. *Leukemia*. 2004;18:113-119.
- Giagounidis AA, Germing U, Wainscoat JS, Boulwood J, Aul C. The 5q-syndrome. *Hematology*. 2004;9:271-277.
- Giagounidis AA, Haase S, Heinsch M, Gohring G, Schlegelberger B, Aul C. Lenalidomide in the context of complex karyotype or interrupted treatment: case reviews of del(5q) MDS patients with unexpected responses. *Ann Hematol*. 2007;86:133-137.
- Giagounidis AAN, Cazzola M, Fenaux, et al. Management of hematological adverse events in MDS patients treated with lenalidomide. Presented at the 9th International Symposium on Myelodysplastic Syndromes; May 16-19, 2007; Florence, Italy. Abstract P147.
- Giagounidis AAN, Cazzola M, Fenaux, et al. Management of non-hematological adverse events in MDS patients treated with lenalidomide. Presented at the 9th International Symposium on Myelodysplastic Syndromes; May 16-19, 2007; Florence, Italy. Abstract P148.
- Crane E, List A. Lenalidomide: an immunomodulatory drug. *Future Oncol*. 2005;1:575-583.

# Notes

---

