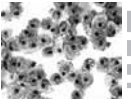


*Myelodysplastic Syndromes:  
Enhancing Treatment  
Outcomes in  
Lower-Risk Patients*

*An Interview with*  
**Mikael A. Sekeres, MD, MS**  
Cleveland Clinic Taussig Cancer Institute





## Journal Club

# *Myelodysplastic Syndromes: Enhancing Treatment Outcomes in Lower-Risk Patients*

### ■ Introduction

Myelodysplastic syndromes (MDS) are a heterogeneous group of bone marrow disorders characterized by bone marrow failure and the propensity to develop acute myelogenous leukemia (AML).<sup>1,2</sup> Clinically these disorders involve ineffective hematopoiesis, leading to frequent need for blood product transfusions.<sup>1,2</sup>

MDS is diagnosed in 3.4:100,000 U.S. citizens, translating to approximately 10,000 new cases each year.<sup>1,2</sup> The median age at diagnosis is approximately 71 years old and the median age of those living with the disease is 72 to 75 years old.<sup>1,2</sup> Furthermore, 55% of cases occur in men and approximately 90% of MDS is primary (*de novo*) disease; 10% is secondary MDS, commonly arising from prior chemotherapy or radiation therapy.<sup>1,2</sup>

Using the International Prognostic Scoring System (IPSS) classification scheme, approximately 75% of newly diagnosed patients and 80 to 85% of established patients have a lower-risk subtype.<sup>3</sup>

For these lower-risk patients, hematology/oncology practitioners have several treatment options: “watchful waiting,” blood product transfusions, growth factor support with erythropoiesis stimulating agents (ESAs), immunosuppression with anti-thymocyte globulin, immunomodulation with lenalidomide, and methyltransferase inhibitors. Yet clinicians have many pragmatic questions regarding place of each therapy, timing, monitoring issues, side effects and their management, administration issues, and patient access.

This edition of *JournalClub*, titled *Myelodysplastic Syndromes: Enhancing Treatment Outcomes in Lower-Risk Patients*, features an interview with Mikkael A. Sekeres, MD, MS, Associate Professor of Medicine at the Cleveland Clinic Taussig Cancer Institute. Dr. Sekeres brings significant experience in the management of MDS, including several seminal publications in 2008. In this edition, as we interview Dr. Sekeres, we will examine issues related to diagnosis and classification, treatment options, and management of lower-risk MDS. The discussion will cover recent publications and put forth practical strategies to optimize the management of lower-risk patients.

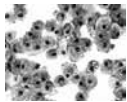
### ■ Accreditation Information

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IMS designates this educational activity for a maximum of one (1) AMA PRA Category 1 Credit™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

### ■ Statement of Need

Between 68 to 71% of MDS cases are low risk.<sup>3</sup> Proper diagnosis and classification are needed to make appropriate treatment choices. Clinicians have available new therapy options. Awareness of emerging data, changing treatment strategies (e.g., advancing survival), the need for a full course of therapy, and practical management strategies are critical to optimizing treatment outcomes.



## ■ Learning Objectives

1. Accurately diagnose, stage, and classify low-risk MDS
2. Define optimal therapy goals
3. Identify effective treatment options, and data
4. Delineate plans for safe and effective administration, monitoring outcomes, and ensuring full treatment courses and response
5. Discuss reimbursement and access strategies

## ■ Target Audience

This publication is specifically designed for practicing clinicians, hematologist/oncologists, and medical oncologists who wish to review and update their knowledge regarding the identification, classification, and management of low-risk myelodysplastic syndrome patients.

## ■ Faculty Disclosure

As an accredited provider of CME, IMS is required to ask faculty to disclose any real or apparent conflict of interest related to presentation and discussion content. The existence of commercial or financial interests of faculty related to the subject matter of this discussion should not be construed as implying bias or decreasing the value of the information shared. However, disclosure should help participants form their own judgments. Resolution of any faculty conflict of interest has been accomplished through review of the program content by the CME provider.

**Mikkael A. Sekeres, MD, MS**

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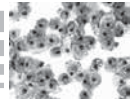
## ■ Corporate Sponsor

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## ■ Release and Expiration Date

**Release Date: April 15, 2009**

**Expiration Date: April 15, 2010**



## ■ How to Obtain CME Credit

To successfully complete this activity, IMS requires that you read the learning objectives, read the monograph, and take the post-test on page 21. You may complete an evaluation and request a CME certificate by going to [www.mdsjournalclub.org](http://www.mdsjournalclub.org). Alternatively, the attached evaluation and CME request can be completed and mailed or faxed to:

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## ■ Keywords

Myelodysplastic syndrome, hematopoiesis, anemia, platelets, International Prognostic Scoring System, transfusions, low-risk, erythropoiesis stimulating agents, immunosuppression, anti-thymocyte globulin, immunomodulation, lenalidomide, methyltransferase inhibitors.

## ■ Disclaimer

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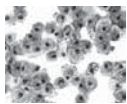
## ■ Faculty Biography



Mikkael A. Sekeres, MD, MS, is an Associate Professor of Medicine at the Cleveland Clinic Taussig Cancer Institute.

Dr. Sekeres received his medical degree and a Masters of Science in Clinical Epidemiology from the University of Pennsylvania School of Medicine in 1996. He completed his Internal Medicine Residency at the Massachusetts General Hospital in 1999 and a Hematology-Oncology Fellowship at the Dana-Farber Cancer Institute in 2002. Dr. Sekeres joined the Cleveland Clinic Lerner College of Medicine of Case Western Reserve University and the Taussig Cancer Institute in 2003.

Dr. Sekeres has been active in the hematology/oncology community with memberships in the American Society of Clinical Oncology, American Society of Hematology, and the Southwest Oncology Group-Leukemia section. He has been actively involved with the Aplastic Anemia and Myelodysplastic Foundation, as a Co-Chair for the Medical Advisory Board and Scientific Committee. He has been a primary investigator for numerous trials involving MDS and other hematologic malignancies. Dr. Sekeres lectures extensively both nationally and internationally on these topics. Dr. Sekeres has over 70 publications, three books, and 68 abstracts to his credit, and is an active reviewer for a dozen publications. This past year, Dr. Sekeres published several seminal papers specific to myelodysplastic syndromes.



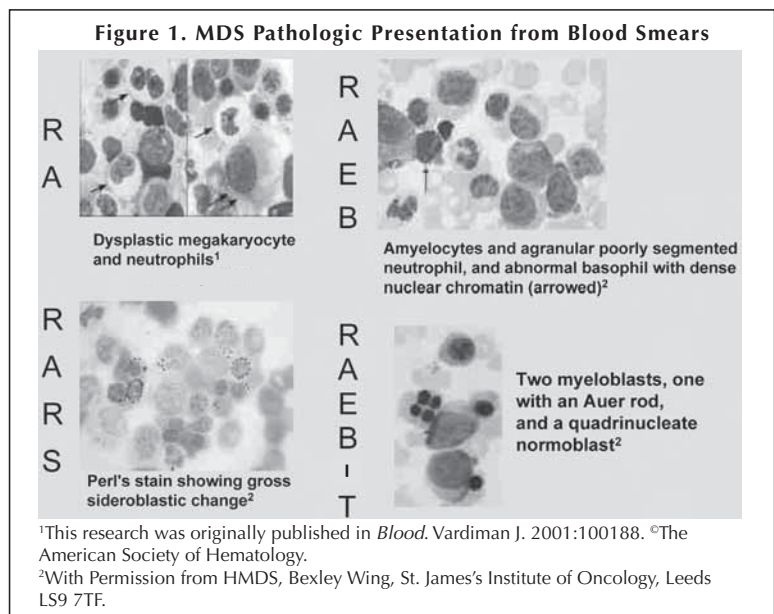
## Interview

**Q** *What clinical signs and laboratory results should hematologists and oncologists use to diagnose and classify lower-risk patients?*

### Clinical Presentation

**DR. SEKERES:** Commonly a patient is discovered to have MDS when he or she goes to a primary care physician with generalized, non-specific complaints including fatigue, loss of appetite, and weight loss. Eventually one goes through routine evaluations for these symptoms: electrocardiogram (ECG), blood loss evaluation (i.e., endoscopy), thyroid assessment, and a complete blood cell count (CBC).

The most common blood manifestation of these patients is to have some form of anemia. Patients at this point often are referred to a hematologist, who evaluates a blood smear and performs a bone marrow biopsy, which provides definitive evidence for proper diagnosis and staging. Typical pathology is illustrated in Figure 1.



### Classification and Staging

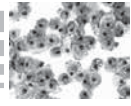
**Table 1. French-American-British (FAB) Classification for MDS**

Classification	Characteristics
Refractory anemia (RA)	Cytopenia of 1 PB lineage; normo- or hypocellular marrow with dysplasias; <1% blasts in PB and <5% bone marrow blasts
Refractory anemia with ringed sideroblasts (RARS)	Cytopenia and dysplasia, with same percentage blast involvement as RA; >15% ringed sideroblasts in bone marrow
Refractory anemia with excess blasts (RAEB)	Cytopenia of ≥ 2 PB lineages; dysplasia involving all 3 lineages; <5% PB blasts and 5-20% bone marrow blasts
Refractory anemia with excess blasts in transformation (RAEB-t)	Same hematologic features as RAEB. >5% blasts in PB or 21-30% blasts in bone marrow or presence of Auer rods in blasts
Chronic myelomonocytic leukemia (CMML)	Monocytosis in PB; <5% blasts in PB and up to 20% bone marrow blasts

PB, peripheral blood.

Adapted from Catenacci DV, Schiller GJ. Myelodysplastic syndromes; a comprehensive review. *Blood Rev.* 2005; 19(6):301-319. Reprinted with permission. ©2005 Elsevier.

Classification for MDS has been based on the French-American-British (FAB) and World Health Organization (WHO) systems.<sup>4</sup> According to the FAB system (Table 1, Figure 1), lower-risk MDS includes patients with a diagnosis of refractory anemia, refractory anemia with ringed sideroblasts, and a subset of patients with chronic myelomonocytic leukemia. Within the WHO classification, lower-risk MDS patients are considered to have any of those categories other than refractory anemia with excess blasts I or II.<sup>5</sup>



The International Prognostic Scoring System (IPSS), a prognostic scoring system published in 1997 by Peter Greenberg, MD (Table 2) is commonly used for clinical trial enrollment, prognosis, and to assist with choice of therapy.<sup>6</sup> This system is based on bone marrow blast percentages, numbers and degrees of cytopenias, and cytogenetics. It divides MDS into four subtypes: low-risk disease, intermediate-1 risk disease, intermediate-2 risk disease, or high-risk disease. Lower-risk disease includes those classified as low or intermediate-I, with a combined IPSS score of 1.0 or lower.

**Table 2. International Prognostic Scoring System (IPSS) for MDS**

Prognostic Variable	Survival and AML Evolution Score				
	0	0.5	1.0	1.5	2.0
Bone marrow blasts (%)	<5	5–10	—	11–20	21–30
Karyotype*	Good	Intermediate	Poor	—	—
Cytopenias**	0 or 1	2 or 3	—	—	—

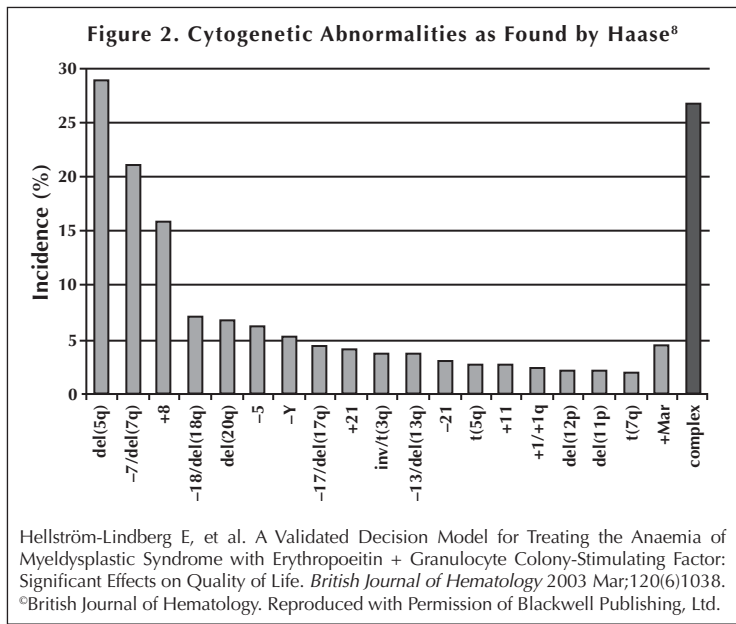
*\*Good = Normal or any 1 of the following: deletion Y, deletion 5Q, deletion 20Q; Intermediate = other abnormalities; Poor = complex (≥ 3 abnormalities) or chromosome 7 abnormalities.*  
*\*\*Cytopenias: neutrophil count <1500/μL, platelets <100,000/μL, hemoglobin <10 g/dL.*

	IPSS Risk Category			
	Low	INT-1	INT-2	High
Combined score	0	0.5–1.0	1.5–2.0	≥ 2.5
AML evolution	19%	30%	33%	45%
Median time to AML (Yr)	9.4	3.3	1.1	0.2
Median survival (Yr)*	5.7	3.5	1.2	0.4

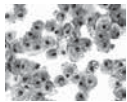
*INT-1, intermediate-1; INT-2, intermediate-2; AML, acute myelogenous leukemia.*  
 This research was originally published in Greenberg P, Cox C, LeBeau MM, et al. International scoring system for evaluating prognosis in myelodysplastic syndromes. *Blood* 1997;89(6):2079-2088. Reprinted with permission. ©1999 American Society of Hematology

**Q** What are some of the specific cytogenetic abnormalities a practitioner might see in a lower-risk patient?

**DR. SEKERES:** The largest grouping of cytogenetic abnormalities was published by Haase et al., based on over 2,000 cases (Figure 2).<sup>7</sup> Approximately 50% of their patients had cytogenetic abnormalities. Among those patients, the most commonly detected one was the deletion 5Q abnormality, occurring in 29% of patients with cytogenetic abnormalities, or 14% to 15% of patients overall. Other common abnormalities included the deletion 7Q, +8, and complex cytogenetics. A full list of common cytogenetic alterations can be found in Table 3.



Patients with lower-risk disease are more likely to have normal cytogenetics, or what are considered good risk cytogenetics. These can include deletion 20Q, deletion 5Q, or a deletion Y chromosome abnormality.<sup>6</sup>



**Table 3. Common Cytogenetic Alterations in MDS**

MDS Subtype	Frequency	Chromosomal Aberrations
RA	25%	deletion 5Q, deletion 20Q, deletion Y, deletion 7, +8
RARS	10%	deletion 5Q, deletion 20Q, deletion Y, deletion 7, +8, idic(X)(q13)
RCMD	50%	deletion 5Q, deletion 7, +8
RCMD-RS	50%	deletion 5Q, deletion 7, +8
RAEB-1	50%	deletion 5Q, deletion 7, +8, deletion 20Q
RAEB-2	50-75%	deletion 5Q, deletion 7, +8, deletion 17p, deletion 11Q, t(11q23), deletion 13, deletion 13Q
MDS deletion 5Q	100%	deletion 5Q

Adapted from Malcovati L, Nimer S. Myelodysplastic Syndromes: Diagnosis and Staging. Cancer Control 2008. 15(4S):4-13. With permission from Cancer Control: Journal of the H. Lee Moffitt Cancer Center and Research Institute. ©2008.

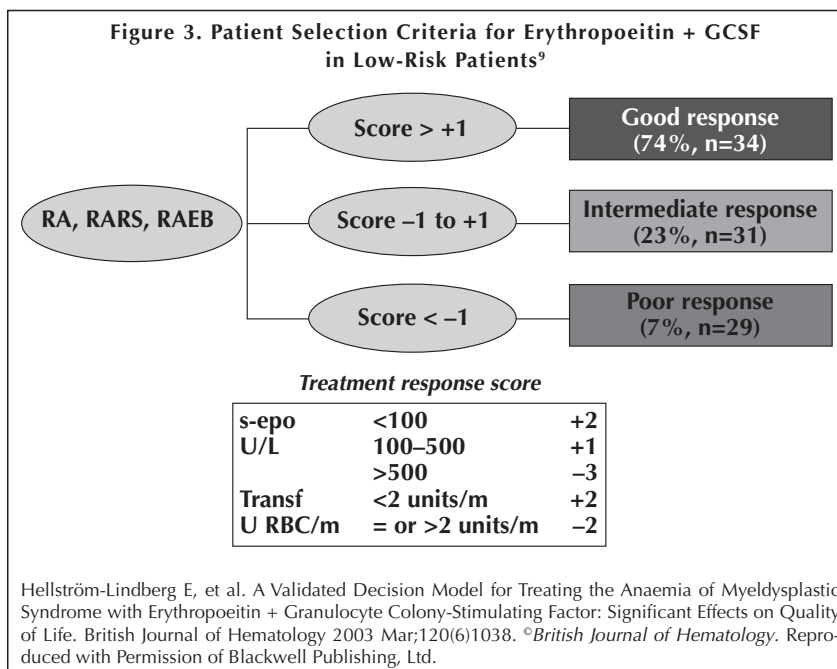
## Q What treatment goals should clinicians consider for lower-risk patients?

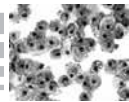
**DR. SEKERES:** In many lower-risk patients who do not present with any blood count abnormalities requiring transfusions, and who have an overall good quality of life, we begin with watchful waiting.

Once blood transfusions (commonly red blood cells) are required, then some form of therapy should be considered. Among newly diagnosed patients with lower risk disease, approximately 22% are dependent on red blood cell transfusions and 6% require platelet transfusions.<sup>3</sup> In these patients, there are several goals—decrease transfusion requirements, improve quality of life, and ultimately increase survival.

## Erythropoiesis Stimulating Agents

**DR. SEKERES:** Often, the initial treatment approach in transfusion-dependent patients includes the use of erythropoiesis stimulating agents (ESAs). Hellström-Lindberg et al. found that patients had different likelihood of responding to ESAs based upon baseline serum erythropoietin (epo) level and transfusion needs (Figure 3).<sup>9</sup> In a decision analysis published by our group that incorporated ESA and other drug response rates along with survival and quality of life, we developed a treatment algorithm based on the Hellstrom-Lindberg response





**Table 4. Decision Analysis with ESAs**

Author	Key Observation/Recommendation
Hellström-Lindberg <sup>9</sup>	<ul style="list-style-type: none"> <li>• Low Serum epo level upon presentation &lt;100 and few transfusion needs <b>74% response rate</b></li> <li>• High serum epo level and transfusion need <b>7% response rate</b></li> <li>• Mixed picture—high serum epo level/low transfusion needs or low serum epo level/high transfusion need <b>23% response rate</b></li> </ul>
Sekeres <sup>10</sup>	<p><b>ESA Treatment to Maximize Survival</b></p> <ul style="list-style-type: none"> <li>• Patients in the high growth factor predictive group, where their serum epo levels are low and transfusion needs are low</li> </ul> <p><b>Non-Growth Factor Treatment</b></p> <ul style="list-style-type: none"> <li>• Patients where transfusion needs are high and their serum epo level is high</li> <li>• Patients who present with a mixed picture</li> </ul>

*epo: erythropoietin*

categories (Table 4).<sup>10</sup> Furthermore, studies by Golshayan et al.<sup>11</sup> and Jadersten et al.<sup>12</sup> have demonstrated that growth factor therapy with ESAs can prolong survival in lower-risk patients.



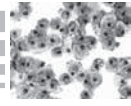
*What other treatment approaches should a clinician use in low-risk-patients?*

**DR. SEKERES:** Once a lower-risk patient has become transfusion dependent, or has symptoms due to MDS and ESAs have failed to work or are unlikely to work, we move into the realm of non-growth factor approaches.

### *Immunosuppressive Therapy with Anti-thymocyte Globulin*

One of these approaches can include immunosuppressive therapy with anti-thymocyte globulin (ATG). Hematopoietic impairment in MDS may arise in part from an aberrant autoimmune process linked to clonal expansion of hematopoietic inhibitory T-lymphocytes.<sup>13</sup> ATG can abrogate this hematopoietic suppression, resulting in hematologic improvement in a select population of patients.<sup>14</sup>

In European and US studies, response rates overall have been in the 30% to 40% range with ATG.<sup>15,16</sup> Molldrem et al. observed that one 4-day course of ATG along with prednisone induced transfusion independence in 34% of patients, with 76% of responding patients maintaining freedom from transfusion at five years of follow-up. Regression analysis showed that younger age and lower platelet count were associated with higher probability of response.<sup>15</sup> Lim et al. confirmed lower IPSS score as a predictor of response, as well as bone marrow hypocellularity.<sup>16</sup> Hematologic response was similar to results from the National Institutes of Health (NIH) experience, in which 75% of patients who responded to ATG sustained a durable response lasting a median of 31.5 months.<sup>16</sup>

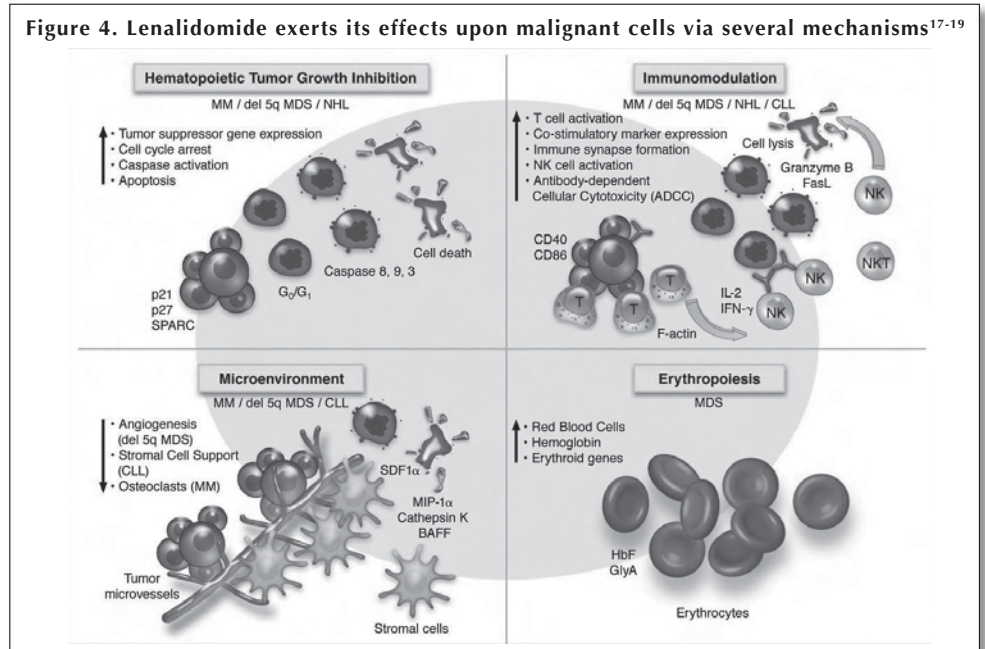


## Immunomodulation with Lenalidomide

For lower-risk patients with the deletion 5Q abnormality who are transfusion dependent, there is one drug, lenalidomide, approved by the Food and Drug Administration. This agent appears to exert its effects via several mechanisms (Figure 4).<sup>17-19</sup>

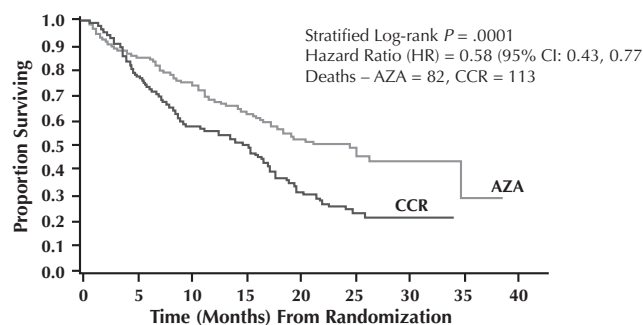
In the registration study (MDS-003), transfusion independence was attained in 67% of 148 patients enrolled.<sup>20</sup> The median duration of transfusion independence in this study and for deletion 5Q patients in other lenalidomide trials was 2.2 years.<sup>20, 21</sup> Approximately 74% of patients in the registration study (MDS-003) had been treated with ESAs in the past. Interestingly, 44% of patients in this study achieved a complete cytogenetic remission, indicating a direct, cytotoxic effect upon the MDS clone.

In another Phase 2 study of lenalidomide in lower-risk, transfusion-dependent patients who did not harbor the deletion 5Q cytogenetic abnormality (MDS-002), transfusion independence response rates were 26%, with a median duration of transfusion independence of 41 weeks.<sup>22</sup>



## DNA Methyltransferase Inhibitors

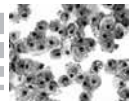
**Figure 5. Overall survival with azacitidine (AZA) compared to CCR in Int-2, High-Risk MDS Patients<sup>23</sup>**



This research was originally published in *Blood*. From Fenaux P, Mufti GJ, Santini V, et al. Azacitidine (AZA) treatment prolongs survival (OS) in higher-risk MDS patients compared with conventional care regimens (CCR): results of the AZA-001 phase III study. *Blood* 2007; 110:250a. Abstract 817. ©2008 American Society of Hematology. Reprinted with permission.

Another option for patients with lower-risk MDS involves the use of DNA methyltransferase inhibitors (DMTIs; azacitidine and decitabine). While these agents are more commonly used in higher-risk patients, activity has been observed in lower-risk patients.<sup>23</sup> Thus, these agents would be appropriate to consider in those who have failed other therapies.

DMTIs have been found preliminarily to improve survival in higher-risk patients. Fenaux et al. reported that azacitidine was superior to conventional care regimens (best supportive care plus low dose cytarabine, or standard chemotherapy), with use of



the drug resulting in a median survival of 24.4 months, versus 15 months for conventional care regimens ( $p=0.0001$ ) and extended overall survival by 74% (HR=0.58; 95% CI: 0.43–0.77) (Figure 5).<sup>23</sup> We await additional studies to see whether such observations may apply to lower-risk patients.

This agent demonstrated a particular efficacy in patients with chromosome 7 abnormalities, previously considered a high-risk cytogenetic group, and may be appropriate as front line therapy in lower-risk patients with this cytogenetic abnormality.<sup>23</sup>

## Bone Marrow Transplantation

**DR. SEKERES:** The only curative therapy for MDS involves stem cell transplantation. Unfortunately, it is only being considered as a treatment option, or performed, in fewer than 5% of MDS patients.<sup>3</sup> This practice is true even in the era of reduced intensity conditioning regimens. Reasons for this low number include the advanced age of most patients, co-morbidities of patients or related donors, and that siblings may not be alive at the time when transplantation is being considered.

If it is decided to treat a patient prior to transplantation, approaches can include chemotherapy or DMTIs. Most consider transplantation to be an up-front option only in higher-risk MDS patients, whereas in lower-risk patients, it should be delayed until other therapeutic options are exhausted.

## Q What about monitoring for safety and efficacy?

**DR. SEKERES:** Once a non-growth factor therapy is started, a patient should be monitored fairly closely during the first two months to assess for therapy-related toxicities, including cytopenias. Patients on ESAs should be monitored for response and possible dose-escalation.

## ESAs

Patients on ESAs (Table 5) should be monitored with a CBC at least every time the patient receives this treatment, which can be as frequent as once weekly. Patients should be initiated on

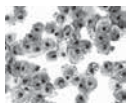
Consideration	Recommendation
Initiation	• Hemoglobin is below 10 grams/dL and present with symptoms.
Target	• 10–12 grams/dL
Monitoring	• CBC at least every time the patient receives this treatment, as frequent as once weekly.
Stopping	• Hemoglobin rises above 12 grams/dL

*CBC: Complete Blood Count, ESA: Erythropoiesis stimulating agents*

an ESA once their hemoglobin falls below 10 and they have symptoms.<sup>25,26</sup> Treatment should be continued as the hemoglobin is maintained at a level between 10 to 12 grams/dL.<sup>25,26</sup>

Therapy should be held once hemoglobin rises above 12 grams/dL.<sup>26</sup> Although an increase in mortality has been observed in some cancer patients with non-myeloid malignancies, a high hemoglobin level has never been

demonstrated to increase such risk in MDS patients.<sup>26</sup> Nonetheless, we still remain cautious with MDS patients and do not allow the hemoglobin to get too high.



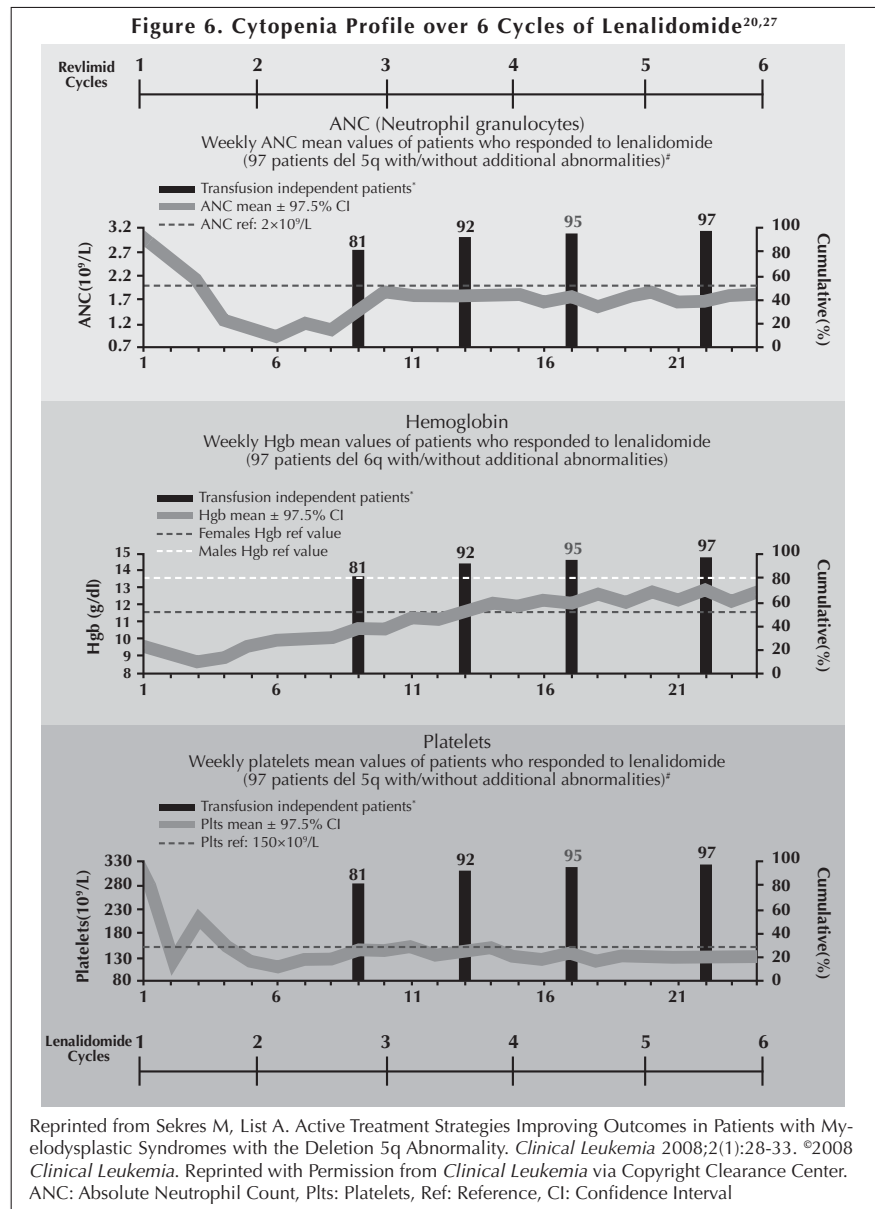
## Lenalidomide

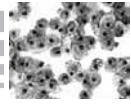
For patients on lenalidomide, particularly with the deletion 5Q abnormality, one of the major side effects is the development of therapy-related cytopenias (Figure 6).<sup>27</sup> This can occur quickly and profoundly. Patients can drop to less than 20% of their baseline value of neutrophils and platelets within the first eight weeks.<sup>20,27</sup> For this reason, they should receive CBCs at least weekly to check for cytopenias and the need for transfusions. Counts will rebound in patients responding to the drug, but still may continue at a level between 20% to 30% of baseline potentially long term.<sup>27</sup>

Interestingly, the development of cytopenias may actually predict for a subsequent transfusion independence response of red blood cells.<sup>28</sup> In deletion 5Q patients who did not have baseline thrombocytopenia and whose platelet count decreased by 50% or greater, 75% ultimately achieved a red blood cell transfusion independence response, versus 47% of patients who did not drop their platelet count by 50% or greater.<sup>20,27</sup> Among those patients with baseline thrombocytopenia who dropped their platelet count by 50% or greater, 58% achieved transfusion independence, versus 33% of patients who did not drop their platelet count by 50% or greater.<sup>27</sup>

Among those patients without baseline neutropenia who dropped their neutrophil count by 75% or greater, 82% achieved a transfusion independence response involving red blood cells versus 51% of those patients who did not drop their neutrophil count by that amount.<sup>27</sup> In patients without baseline neutropenia, the development of treatment-related neutropenia did not predict for subsequent red blood cell transfusion independence.<sup>27</sup>

These results held up in multivariate analyses and were found to significantly correlate with a cytogenetic response. Key predictors<sup>27</sup> of response have been summarized in Table 6.





**Table 6. Key Predictors of Response**

Parameter	Response Predictor
Decrease in Platelets	≥ 50% vs. < 50%)
Decrease in ANC	≥ 75% vs. < 75% (without baseline neutropenia)
Transfusion Burden	≤ 4 RBC Units/8 Weeks vs. > 4 RBC Units/8 Weeks
Duration of MDS before Study Entry	≤ 2 Years vs. > 2 years

ANC: Absolute Neutrophil Count, MDS: Myelodysplastic Syndromes, RBC: Red Blood Cell

**Q** *How long should clinicians treat MDS patients with immunomodulation therapy such as with lenalidomide?*

**DR. SEKERES:** Lower-risk disease is not a rapidly progressive cancer. It can be more analogous to chronic leukemia. A critical point to recognize is that as lower-risk disease can be slow to develop, it may also be slow to respond to therapies. When I am treating a patient with lower-risk disease, with any type of therapy, my approach is to give them that treatment for at least four months (Figure 6). Ninety percent of patients with lower-risk disease will respond to a therapy, if they are going to respond, within four months of starting.<sup>27,28</sup>

I do believe that clinicians are doing a disservice to their MDS patients by stopping drug solely because of therapy-related cytopenias, especially prior to four months. Cytopenias may predict for drug response, especially in deletion 5Q patients. So stopping drug prematurely may compromise patient outcomes.

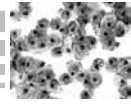
**Q** *What strategies should clinicians utilize to help patients through cytopenias for four months or longer of treatment?*

**DR. SEKERES:** What I typically do with a deletion 5Q patient is to start lenalidomide 10

mg daily for 28 out of 28 days (Table 7).<sup>29</sup> If my patient develops severe cytopenias (a drop to 20% of baseline of neutropenia or thrombocytopenia), my first approach, for example, in the case of severe neutropenia, would be to monitor the patient closely for any signs of infection and to consider use of an adjunctive growth factor to increase neutrophil counts.<sup>29</sup> (There were 12 patients on the MDS-003 study who received a granulocyte colony stimulating factor<sup>20</sup>).

**Table 7. Dosing Considerations and Cytopenia Management with Lenalidomide<sup>29</sup>**

Consideration	Recommendation
Initial Dosing	<ul style="list-style-type: none"> <li>• 10 mg daily for 28 out of 28 days</li> </ul>
Severe cytopenias (20% of baseline)	<p><b>Neutropenia</b></p> <ul style="list-style-type: none"> <li>• Monitor patients closely for any signs of infection</li> <li>• Consider use of an adjunctive growth factor to increase neutrophil counts</li> </ul> <p><b>Thrombocytopenia</b></p> <ul style="list-style-type: none"> <li>• Platelet transfusion during first couple months of therapy</li> </ul>
Patient actively bleeding and not responding well to platelet transfusions	<ul style="list-style-type: none"> <li>• Initial dose reduction to 5 mg daily</li> </ul>
Patient who develops signs of infections	<ul style="list-style-type: none"> <li>• If profound, symptomatic cytopenias persist, one further dose reduction at 5 mg every other day can be made</li> </ul>



For patients who develop severe thrombocytopenia, I would actually consider transfusing with platelets to try to bolster them during the first couple months of therapy.<sup>27,29</sup>

If the patient is actively bleeding and not responding well to platelet transfusions, or a patient does start to develop signs of infections with neutropenia, then I would consider reducing the dose to 5 mg daily, as was the case with 84% of patients enrolled on the lenalidomide registration study.<sup>20</sup> If a patient continues to have profound, symptomatic cytopenias after that dose reduction, one further dose reduction at 5 mg every other day can be made.<sup>29</sup>

### *In those patients on DMTIs, what should clinicians look out for?*

**DR. SEKERES:** While most of the DMTI experience is in patients with higher-risk disease, many of the same principles relative to response and to cytopenias apply. Ninety percent of patients who respond to a DMTI do so within six months of therapy, so it is critical to maintain treatment for this time period.<sup>30</sup> While patients in the registration study by Silverman et al. developed grade III or IV neutropenia or thrombocytopenia, these were expected and were not a reason to discontinue therapy prematurely.<sup>31</sup>

### *What are some of the practical issues that hematology/oncology specialists should consider?*

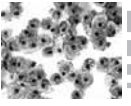
#### *Medication Access with Oral Agents*

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**DR. SEKERES:** As the median age is 71 years at diagnosis,<sup>3</sup> most of these patients will be on Medicare. Issues that do arise include whether a patient has prescription coverage for an oral drug and if one has enough money to get through the “donut hole.” These are items that need to be discussed with the patient upfront.

We explore different avenues for helping with paying for medication. These can range from checking to make sure a patient can afford drug copayment, looking to societies (e.g., Aplastic Anemia and MDS International Foundation; Leukemia/ Lymphoma) that may help with medication payment, and appealing directly to the company for patient assistance. Many companies have reimbursement hotlines, which can be very helpful. In using one of these approaches, I have had success in with getting drugs covered most of the time.

Access to needed medications can be a challenge to patients. This consideration can be a concern, particularly with those on Medicare Part D who reach the “donut hole.” In 2008, this gap was \$4,050 and has increased \$300 to \$4,350 in 2009.<sup>32</sup> To streamline the process and obtain funds from the variety of available resources for high co-payments, there are specialty pharmacies which have relationships with companies where they may have other avenues for a system with payment. Such pharmacies can act as a “virtual” assistant to help facilitate and complete prior authorizations along with required paperwork for funding rapidly at NO additional charge.



## *Administration*

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**DR. SEKERES:** There is the issue with subcutaneous injections. DMTIs can be associated with erythema and injection site reactions; however, I have never had a patient stop therapy with a DMTI as a result. My nurses advise patients to use either hot or cold compresses, or to use topical steroids.

Another strategy is to identify a nurse in a clinic who is going to be the DMTI injection specialist. That person is going to eventually have more skill at giving it and is going to be better at giving it.

## *Scheduling*

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With DMTI therapy, a 7-day administration can be a real challenge, particularly for clinics not open on weekends. There are alternative dosing strategies, including 5-day dosing as reported by Lyons et al., which appears to show no difference in response rate.<sup>33</sup> Our clinic is closed on Sundays so we utilize a 6-day dosing schedule. Some practitioners will give it for five days in a row, then have a patient come back on a Monday and Tuesday the next week.<sup>33</sup>

## *Pharmacy Ordering*

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In our clinic, we have an individual who deals with specialty drugs like lenalidomide. This specialist takes the prescription and then coordinates with specialty pharmacies, helps patients get through programs like RevAssist®, where a patient needs to be registered to receive a drug. It is critical to identify within one's clinic an individual who is used to navigating all of this paperwork.

## *What communication strategies should clinicians utilize when managing their MDS patients?*

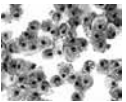
**DR. SEKERES:** The most important thing is that once a patient is started on a non-growth factor approach, practitioners should maintain close contact with them. If a treatment is going to have some effect on the disease, it may also cause side effects. One of the major reasons patients stop treatment is because they have not seen their doctor for four weeks, have significant side effects, and feel they do not have anyone to talk with about what is occurring. Close contact, particularly during the first eight weeks of therapy, is crucial in managing side effects and expectations.

Along those lines, regular communication within the healthcare team, particularly with one's pharmacist and nurse, is critical to review and discuss monitoring, preparation, scheduling, ordering, and reimbursement issues.



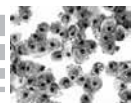
## *Key Learning Points*

- MDS is more prevalent than we know. Cytopenias are not just a normal consequence of aging and should be evaluated with a bone marrow biopsy.
- Therapies for lower-risk disease may capitalize on maximizing production of the remaining normal stem cells from the bone marrow, abrogating the apoptotic effects of the bone marrow microenvironment.
- Treatments have become more personalized to the signature of a patient's disease, such as lenalidomide for deletion 5Q patients.
- Therapy-related cytopenias are predictive for subsequent response and not be looked at as an undesirable adverse event. These patients can be maintained during first four months of therapy with careful monitoring and cytopenia management strategies.
- Maintenance of patients on therapy is dependent on close patient contact within the first eight weeks of therapy. Communication among members of the team caring for these patients is critical for treatment access, proper administration, monitoring, and management of side effects to optimize treatment outcomes.

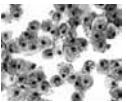


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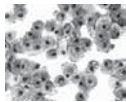
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Two recent clinical articles relevant to the management of MDS can be requested through Diplomat Specialty Pharmacy by checking (✓) the following:

- List A. Treatment Strategies to Optimize Clinical Benefit in the Patient With Myelodysplastic Syndromes. *Cancer Control* 2008, 15,(4S):29-39.
- Sekeres M, List A. Active Treatment Strategies Improving Outcomes in Patients with Myelodysplastic Syndromes with the Deletion 5q Abnormality. *Clinical Leukemia* 2008. 2(1):28-33.

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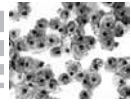
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**Dr. Sekeres is available to respond to your specific questions related to myelodysplastic syndrome. Please feel free to email him at: SEKEREM@ccf.org**

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◆ **Post-Test** *Please cut out or photocopy and include with Program Evaluation.*

1. Typical initial complaints of low-risk MDS includes all of the following except?
  - a. Fatigue
  - b. Bleeding
  - c. Loss of appetite
  - d. Weight loss
2. What is most true regarding low-risk patient classification?
  - a. Combined score <.5
  - b. Combined score ≤ 1
  - c. Leukemic death in a third of patients
  - d. Median survival of 3.5 years
3. Definitive diagnosis of low-risk MDS is based upon:
  - a. Hg
  - b. CBC
  - c. Clinical symptoms
  - d. Bone marrow aspirate and biopsy
4. Lower-risk disease represents approximately \_\_\_% of newly diagnosed MDS patients:
  - a. 25%
  - b. 50%
  - c. 70%
  - d. 90%
5. Among patients with cytogenetic abnormalities, the most common is:
  - a. Deletion 7Q
  - b. +8
  - c. Complex
  - d. Deletion 5Q
6. Treatments options for lower-risk MDS include:
  - a. Best supportive care
  - b. Transfusions
  - c. Erythropoiesis stimulating agents
  - d. Lenalidomide
  - e. Methyltransferase inhibitors
  - f. All the above
7. Active treatment with a therapeutic for lower-risk patients begins upon:
  - a. Diagnosis and staging
  - b. The need for transfusion or development of symptoms
  - c. Identification of cytogenetic abnormality
  - d. Progression to higher-risk disease
8. Which is not true with erythropoiesis stimulating agents
  - a. Used when Hg <10 grams/dL
  - b. Target Hg 10-12 grams/dL
  - c. Not to exceed 12 grams/dL
  - d. Responses with high serum epo level and transfusion need
  - e. Response is maximized in patients where transfusion needs are high and their serum epo level is high
9. Immunomodulatory treatments like lenalidomide:
  - a. Are effective in deletion 5Q and non-deletion 5Q low-risk patients
  - b. Causes transfusion independence in deletion 5Q patients
  - c. Work through several mechanisms of action
  - d. Should be utilized for at least four months to maximize response
  - e. Are associated with cytopenias
  - f. All the above
10. Cytopenias with immunomodulatory agents can be managed with:
  - a. Growth factor support
  - b. Transfusions
  - c. Dose reduction
  - d. All the above

*Answer Sheet*

1.	A	B	C	D		
2.	A	B	C	D		
3.	A	B	C	D		
4.	A	B	C	D		
5.	A	B	C	D		
6.	A	B	C	D	E	F
7.	A	B	C	D		
8.	A	B	C	D	E	
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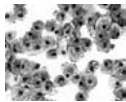
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*Answers: 1.B 2.B 3.D 4.C 5.D 6.F 7.B 8.E 9.F 10.D*

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	Excellent	Very Good	Good	Fair	Poor
Contents					
Style / Clarity					
Overall Format					

	Definitely Yes	Somewhat Yes	Neutral	Somewhat No	Definitely No
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1. Accurately diagnose, stage, and classify low-risk MDS					
2. Define optimal therapy goals					
3. Identify effective treatments options and data					
4. Delineate plans for safe and effective administration, monitoring outcomes, and ensuring full treatment courses and response.					
5. Discuss reimbursement and access strategies.					

Comments: \_\_\_\_\_  
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