



Linda Holmes. *Cassis*. Oil on canvas, 14" × 18".

*Ten questions are answered
on how to use lenalidomide
for myelodysplastic syndromes.*

Practical Considerations in the Use of Lenalidomide Therapy for Myelodysplastic Syndromes

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Lenalidomide has been approved by the US Food and Drug Administration for the treatment of patients with myelodysplastic syndromes (MDS) with an interstitial deletion of the long arm of chromosome 5 and, more recently, in combination with dexamethasone for multiple myeloma in patients who received at least one prior therapy. This discussion examines several clinically relevant, practical considerations regarding dosing, monitoring, follow-up evaluation, adverse events, and available support for lenalidomide recipients and their prescribing physicians in the MDS setting.

Introduction

Lenalidomide (Revlimid[®], Celgene Corp, Summit, NJ), an ImiD[®], is a second-generation immunomodulatory drug and thalidomide derivative that has been extensively studied in patients with myelodysplastic syndromes

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(MDS). Results from these clinical trials have been positive. Key MDS clinical trials reported both an erythroid and a cytogenetic response in up to 83% of study participants, with a median response time as early as 4 weeks after initiating therapy.^{1,2} Further, lenalidomide was identified as more potent than thalidomide and devoid of many of the serious adverse reactions associated with thalidomide administration, such as neuropathy.³ Based on the clinical efficacy of lenalidomide and the manageable dose-dependent myelosuppression, the US Food and Drug Administration (FDA) has approved lenalidomide administration in MDS patients with an interstitial deletion of chromosome 5q [del(5q)].

Within the following discussion, a series of questions examine a number of practical, clinically relevant issues with lenalidomide with regard to its use in MDS.

Topics include patient selection, dosing and monitoring recommendations, potential clinical impact, common and uncommon adverse events, management strategies to address these adverse events, and patient education and support.

Question #1. Which of my patients should be treated with lenalidomide?

Lenalidomide was approved by the FDA in December 2005 for the management of low-and intermediate-1-risk MDS patients with del(5q) following the conclusion of the MDS-001 and MDS-003 clinical trials.^{1,2} These trials found that lenalidomide had substantial activity in MDS, particularly in patients with del(5q). Lenalidomide was also studied in MDS patients without the del(5q) abnormality. While not as impressive as in the del(5q) group, erythroid response rates in MDS patients lacking the cytogenetic abnormality were 43% to 45% in the MDS-001 and -002 clinical trials, respectively. Therefore, those transfusion-dependent patients with del(5q) who have adequate platelet and neutrophil thresholds are candidates for lenalidomide therapy if primary treatment with recombinant erythropoietin fails or appears unlikely to be effective based on high transfusion burden (2 or more units per month) and/or high endogenous erythropoietin concentrations (ie, >500 U/L).

Specific guidelines, including reference to the National Comprehensive Cancer Network (NCCN) treatment algorithm for MDS patients, are presented in question #10.

Question #2. What is the likelihood of benefit?

Based on the MDS-001 and MDS-003 phase I-II clinical studies evaluating the safety and efficacy of lenalidomide

administration in MDS patients, both erythroid and cytogenetic responses have been observed with lenalidomide treatment.^{1,2} In the MDS-001 clinical trial, 83% of patients with del(5q) had an erythroid response (major and minor) accompanied by a cytogenetic response rate of 83%. Similarly, the MDS-003 trial reported an erythroid response in 76% of patients with an isolated del(5q) and a cytogenetic response in 73% of patients. This included 45% of patients who experienced a complete cytogenetic response. To date, the impact of lenalidomide on overall survival in MDS patients remains unclear, although preliminary analyses from the MDS-003 trial in patients with deletion 5q and greater karyotype complexity suggest such patients may experience extended survival that exceeds historical expectations.⁴ Clinical studies evaluating the effect of lenalidomide on survival in patients with isolated del(5q) would be challenging, given the long natural history in this population.

Question #3. What dose should I prescribe and how long do I continue treatment? How and when do I evaluate treatment response?

For MDS, the initial recommended dose of lenalidomide per the current FDA-approved package insert defines the recommended dose as 10 mg orally once daily on a continuous dosing regimen. This dose is based on trials by List et al¹ who tested three dosing regimens of lenalidomide in MDS in phase I and II studies. In patients who tolerate lenalidomide well and show clinical benefit from lenalidomide (eg, freedom from transfusions, increased hemoglobin levels), lenalidomide administration can continue indefinitely. Responding patients in the MDS-003 study stayed on drug continuously for a median of 3 weeks prior to their first dose interruption or reduction. This suggests that aggressive hematologic supportive care might aid in maximizing response.

Table 1. — Parameters Involved in Evaluating the Response to Treatment in MDS Patients Receiving Lenalidomide as Defined in the Clinical Trials Described Herein¹

Outcome Measurement	Definition
Major erythroid response	Freedom from the need for transfusion, or an increase in hemoglobin levels of 2 g/dL
Duration of transfusion independence	Calculated from the date of last red blood cell transfusion to the resumption of transfusions
Duration of major responses in transfusion-independent patients	Calculated from the initial date of the sustained elevation in hemoglobin levels of more than 2 g/dL
Minor erythroid response	At least a 50% reduction in transfusions or a sustained hemoglobin elevation of 1–2 g/dL
Partial cytogenetic response	≥50% decrease in abnormal cells in metaphase
Complete cytogenetic response	Complete disappearance of the abnormal cells in metaphase; complete response may also be evaluated by in situ hybridization with the use of the 5q31 (EGR1X2)-specific probe to confirm the absence of the 5q31.1 deletion among 200 cells in interphase

Table 1 defines various endpoints used in evaluating response to lenalidomide for MDS patients. As determined from the results of the clinical trials and the recommendations in the FDA-approved package insert, complete blood counts should be performed weekly for the first 8 weeks and then at least monthly thereafter in MDS patients, given the early myelosuppression expected with suppression of the del(5q) clone. Premature dose interruptions and/or reductions of lenalidomide should be avoided in MDS patients.

Question #4. How is treatment-related myelosuppression addressed? How should I monitor my patients?

Lenalidomide is devoid of many adverse reactions associated with its parent compound thalidomide; however, myelosuppression is a concern. As illustrated in Table 2, neutropenia and thrombocytopenia are the most common serious (ie, grade 3 or greater) adverse reactions expected with lenalidomide therapy in MDS. Not surprisingly, severe neutropenia was more prevalent in the del(5q) MDS subpopulation compared with either the non-del(5q) MDS patients or MM patients. However, experience in the MDS-001 trial indicates that neutropenia can be mitigated with the use of myeloid growth factors without any adverse effect on response. Further, if patients have clinically significant thrombocytopenia (<50,000/ μ L) prior to lenalidomide treatment, thrombocytopenia may pose a serious concern and could affect the safety and duration of lenalidomide treatment necessary to adequately suppress the del(5q) clone in MDS patients. Indeed, List et al² reported that baseline thrombocytopenia was highly predictive of subsequent lower probability of cytogenetic response to lenalidomide in del(5q) MDS patients due to a shorter duration of initial therapy.

Guidelines for managing thrombocytopenia in del(5q) MDS patients have been provided within the

Table 2. — Percentage and Number of 148 MDS Patients Prescribed Lenalidomide Who Experienced Serious (Grade 3 or 4) Adverse Event(s)

Event	No. of Patients (%)
Neutropenia	79 (53.4)
Thrombocytopenia	74 (50.0)
Diarrhea	5 (3.4)
Constipation	0
Pruritus	3 (2.0)
Rash	10 (6.8)
Fatigue	7 (4.7)
Pulmonary embolism	3 (2.0)
Deep vein thrombosis	0

Adapted (with permission) from the FDA-approved Revlimid[®] package insert, current as of July 2006.

FDA-approved package insert for lenalidomide and have been summarized in Table 3. In patients with a baseline platelet count of 100,000/ μ L or higher that decreases to 50,000/ μ L or less within the first 4 weeks of therapy, lenalidomide administration is interrupted until platelet counts exceed 50,000/ μ L. Lenalidomide administration is then resumed at half the dose (5 mg orally once daily). A similar course of action is advised in patients with a low baseline platelet count and in patients who develop thrombocytopenia after 4 weeks of initiating lenalidomide as outlined in Table 3. If thrombocytopenia persists at 5 mg of lenalidomide daily, then further reduction in dose may be warranted.

Similar recommendations have been made regarding the management of neutropenia in del(5q) MDS patients as summarized in Table 4, although myeloid growth factors may be considered before initial treatment interruption for neutropenia. For example, if baseline neutrophil counts exceed 1,000/ μ L then fall below 750/ μ L within the first 4 weeks of treatment, lenalidomide administration is interrupted and resumed at half the daily dose only when neutrophil counts return to 1,000/ μ L or more. In patients presenting with a low neutrophil count at baseline, lenalidomide administration is interrupted when neutrophil counts fall below 500/ μ L. Further dose adjustments may be required in patients with a persistent neutropenia on 5 mg daily if the neutropenia is associated with a fever or if neutropenia develops after 4 weeks of beginning therapy. Cytokine therapies such as myeloid growth factors including G-CSF (granulocyte colony-stimulating factor, filgrastim (Neupogen[®], Amgen, Inc, Thousand Oaks, CA) and pegfilgrastim (Neulasta[®], Amgen, Inc, Thousand Oaks, CA) can be safely administered concurrently with lenalidomide and might limit the severity of neutropenia and the need for repeated dose reductions.

It should be noted that MDS patients receiving lenalidomide may demonstrate sustained, moderate cytopenias that are asymptomatic (ie, thrombocyte levels between 50,000 and 100,000/ μ L; ANC counts between 750 and 1,000/ μ L). These patients do not require dose reduction or interruption.

Question #5. Considering that the thrombogenic potential is amplified by interaction with other agents, particularly in multiple myeloma, including dexamethasone and erythropoietic agents, what should my patients do to avoid this potential complication?

Patients taking lenalidomide should also be made aware that the risk of deep vein thrombosis (DVT) with subsequent pulmonary embolism (PE) is a concern in

patients with multiple myeloma (MM) but is not typically an issue in patients with MDS. Indeed, the results of Study 1 and Study 2 trials reported at the 2005 meeting of the American Society of Clinical Oncology (ASCO) identified an increased risk of DVT and PE in myeloma patients receiving lenalidomide and dexamethasone compared to patients treated with dexamethasone.⁵ Further, in a recent letter to the editor published in the *New England Journal of Medicine*⁶ and presented at the 2006 ASCO meeting,⁷ it was communicated that administration of erythropoietin or other erythropoietic agents should be employed judiciously in MM patients prescribed lenalidomide and dexamethasone

since this drug combination appears to increase the risk for thrombotic events.

If a history of DVT, either personal or familial, is identified or if the patient is sedentary or overweight, then aggressive monitoring during the treatment period is warranted in patients receiving lenalidomide in combination with dexamethasone, recombinant erythropoietins, or any other potentially prothrombotic agent. Patients are advised to consult their physician if they experience any signs of thrombosis, including shortness of breath, chest pain, or swelling of the arm or leg. It is currently unknown if prophylactic anticoagulation therapy lessens the potential for venous

Table 3. — Management of Thrombocytopenia in MDS Patients Receiving Lenalidomide Therapy

Event	Course of Action
Platelet counts drop to <50,000/ μ L <i>within 4 weeks</i> of starting treatment at 10 mg/day	Interrupt lenalidomide administration Resume lenalidomide at 5 mg/day once platelet counts return to >50,000/ μ L
Platelet counts drop to 50% of the baseline value <i>within 4 weeks</i> of starting treatment	Interrupt lenalidomide administration If baseline platelet counts were >60,000/ μ L, then resume lenalidomide administration at 5 mg/day when platelet counts return to >50,000/ μ L If baseline platelet counts were <60,000/ μ L, then resume lenalidomide administration at 5 mg/day when platelet counts return to >30,000/ μ L
Platelets decrease <30,000/ μ L or <50,000/ μ L with platelet transfusions <i>after 4 weeks</i> of lenalidomide at 10 mg/day	Interrupt lenalidomide administration Resume lenalidomide at 5 mg/day when platelets are >30,000/ μ L (without hemostatic failure)
Thrombocyte counts decrease <30,000/ μ L or <50,000/ μ L with platelet transfusions in patients receiving lenalidomide 5 mg/day	Interrupt lenalidomide administration Resume lenalidomide at 5 mg every other day when platelets are >30,000/ μ L (without hemostatic failure)
Adapted (with permission) from the FDA-approved Revlimid® package insert, current as of July 2006.	

Table 4. — Management of Neutropenia During Lenalidomide Administration in MDS Patients

Event	Course of Action
Neutropenia develops <i>within 4 weeks</i> of initiating lenalidomide at 10 mg/day, and neutrophil levels decrease below 750/ μ L	Interrupt lenalidomide administration Resume lenalidomide administration at 5 mg/day once neutrophil counts return to \geq 1,000/ μ L
Neutropenia develops <i>within 4 weeks</i> of initiating lenalidomide in patients with a baseline neutrophil count of <1,000/ μ L, and neutrophils decrease below 500/ μ L	Interrupt lenalidomide administration Resume lenalidomide administration once neutrophil counts return to \geq 500/ μ L at 5 mg/day
<i>After 4 weeks</i> of lenalidomide administration, neutrophil counts drop <500/ μ L for \geq 7 days or if associated with a fever (\geq 38.5°C)	Interrupt lenalidomide administration Resume lenalidomide administration once neutrophil counts return to \geq 500/ μ L at 5 mg/day
Neutrophils decrease below 500/ μ L at 5 mg/day lenalidomide for \geq 7 days or if associated with a fever (\geq 38.5°C)	Interrupt lenalidomide administration Resume lenalidomide administration at 5 mg every other day once neutrophil counts return to \geq 500/ μ L
Adapted (with permission) from the FDA-approved Revlimid® package insert, current as of July 2006.	

thrombotic events. Therefore, careful assessment of each patient's risk factors is warranted.

DVT prophylaxis in patients who have no history of clots and are at low risk of developing clots, administration of cyclooxygenase inhibitors such as aspirin 325 mg daily may be employed. However, careful consideration of risks related to thrombocytopenia is necessary to avoid potential bleeding complications. Further, due to the paucity of prospective, controlled clinical trials, evidence supporting the benefit of prophylactic aspirin (full or low dose) is based primarily on historical experience. Low-molecular-weight heparin or warfarin also may be administered at either prophylactic or therapeutic doses, especially in high-risk patients with or without a history of clots. Close patient monitoring at a coagulation clinic is warranted in these patients on a weekly basis.

Question #6. How do I prevent or manage other treatment side effects?

The most common serious (grade 3 or 4) hematologic and nonhematologic adverse reactions experienced in MDS patients receiving lenalidomide are summarized in Table 2, which shows that adverse events unrelated to myelosuppression are relatively uncommon. Although patients should be educated regarding all potential adverse events, myelosuppression and thrombotic events (DVT and PE rates are increased in multiple myeloma patients taking lenalidomide and dexamethasone) are the most serious adverse events related to lenalidomide administration. The most common non-hematologic adverse events (all grades) experienced by MDS lenalidomide recipients are diarrhea, pruritus, rash (ie, a mild localized urticarial dermatitis or morbilliform eruptions that do not require alterations in lenalidomide dosing), and fatigue.

Question #7. Can other medications be safely administered concurrently with lenalidomide?

In addition to cytokine therapy required to manage severe neutropenia, supplementary medical intervention may be required in patients prescribed lenalidomide. These include platelet transfusions in patients who experience thrombocytopenia and red blood cell transfusions in MDS patients with persistent anemia. In light of the increased risk associated with lenalidomide and dexamethasone administration in MM patients, anticoagulants such as aspirin, warfarin, or heparin can be added to the treatment regimen. Finally, alternate prescription medications or over-the-counter remedies can be indicated for the management of other adverse

events, as described in question #6. According to the FDA-approved package insert, lenalidomide is not metabolized by and does not inhibit or induce the cytochrome P450 pathway and is therefore unlikely to cause any interactions with drugs that do impact this pathway. Further, there is no reported interaction with warfarin or digoxin.⁸

Question #8. What special care is needed for women of childbearing age?

Teratogenicity due to the administration of thalidomide has been well established. While lenalidomide has not been associated with human birth defects, the FDA-approved package insert includes a black box warning regarding the use of lenalidomide in women and men.⁸ Specifically, female patients of childbearing potential require two negative pregnancy tests: the first within 10 to 14 days and the second within 24 hours prior to prescribing lenalidomide. Pregnancy tests are performed weekly during the first 4 weeks of therapy, then monthly in women with regular menstrual cycles.

Furthermore, two forms of birth control, one highly effective (such as oral birth control pills or latex condom) must be used for 1 month before, during, and after lenalidomide treatment. Male patients are advised to always wear a latex condom during sexual contact with women of childbearing potential. It is unknown if lenalidomide is excreted in semen.⁸

Question #9. What should my patients know about lenalidomide therapy and what assistance is available to help my patients have access to lenalidomide?

The most important safety issue relates to birth control. In addition, the issue of myelosuppression is critical in the MDS patient. Patients should have a complete blood count weekly in the first 8 weeks and be instructed to review the results with their providers and report signs or symptoms that may indicate symptomatic thrombocytopenia (bleeding, petechiae, hematuria, hematomas) or neutropenia (fever, chills, sore throat, or progressive cough).

All patients and licensed prescribers must be registered in the RevAssistSM Restricted Distribution Program and comply with the program requirements in order for lenalidomide to be dispensed. Lenalidomide prescriptions can be filled only by one of the approved network pharmacies. The prescription must be sent to the Revlimid[®] registered network pharmacy in order for the drug to be delivered direct to the patient's home.

The major components of the RevAssistSM program include education concerning the risks associated with lenalidomide administration and effective contraception before, during, and after lenalidomide administra-

tion (including times of dose interruption). The patient medication guide, the FDA-approved package insert, www.revlimid.com, and the MDS foundation (www.mds-foundation.org), among others, provide valuable information on these components.

Finally, the Celgene Corporation has a program called PSSSM (Patient Support Solutions) that can help determine qualifications for reimbursement, insurance assistance, co-pay assistance, and therapy assistance. This program is available for patients prescribed lenalidomide in order to allow the greatest number of patients as possible access to this drug.

Question #10. What are the best guidelines to help me decide where lenalidomide fits in overall management?

In response to the FDA approval of lenalidomide in del(5q) MDS patients, the National Comprehensive Cancer Network (NCCN)⁹ incorporated the administration of lenalidomide into the treatment algorithm and currently recommends lenalidomide in this subset of MDS patients in their Clinical Practice Guidelines in Oncology (version 4.2006). This treatment algorithm assists physicians in selecting the best possible treatment for their MDS patients based on erythropoietin responsiveness, International Prognostic Scoring System (IPSS), HLA-DR allele, and cytogenetic evaluation. Readers are encouraged to refer to the manuscript focusing on the treatment algorithms of MDS within this supplement.

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