

Practical Management of Lenalidomide-Related Rash

Sara M. Tinsley,¹ Sandra E. Kurtin,² Jean A. Ridgeway³

Abstract

Lenalidomide (LEN) is an immunomodulatory drug with US Food and Drug Administration approval for use in myelodysplastic syndromes (MDS), multiple myeloma (MM), and mantle cell lymphoma (MCL). The toxicity profile for LEN is similar across indications, with the most common adverse events reported in registration trials being hematologic in nature, and Grade ≥ 3 hematologic toxicities the most common reasons for treatment interruption or permanent LEN discontinuation. However, an analysis of the Celgene Global Drug Safety database showed that nonserious rash was the leading cause of permanent early discontinuation of LEN in patients with MDS treated in the postmarketing setting (similar data not available for patients with MM or MCL). In registration trials, rash was reported in up to a third of patients, but Grade ≥ 3 rash was uncommon and rash rarely led to LEN treatment interruption or permanent discontinuation. This suggests differences in management of LEN-related rash in clinical trials versus real-world use. Most LEN-related rash is mild to moderate in severity and might present as patchy, raised, macular skin lesions, sometimes with localized urticaria, which might be associated with pruritus. Mild to moderate rash might be treated with topical corticosteroids and/or oral antihistamines. Any grade LEN-related rash should be appropriately managed through awareness of symptoms, appropriate and prompt intervention, and maximizing patient self-reporting of early signs of rash using upfront educational initiatives. This guide to management of LEN-related rash reviews key clinical data from registration trials, and the incidence and physiology of LEN-related rash, grading of rash, and guidelines for patients and caregivers.

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Introduction

Lenalidomide (LEN) is a novel, oral immunomodulatory drug that is indicated for the treatment of patients with myelodysplastic syndromes (MDS), multiple myeloma (MM), and mantle cell lymphoma (MCL). It was first approved by the US Food and Drug Administration (FDA) in 2005 for treatment transfusion-dependent anemia due to low- or intermediate-1-risk MDS with deletion of 5q (del[5q]) abnormality with or without additional cytogenetic abnormalities. The recommended starting dose is 10 mg daily.¹ In 2006, LEN was approved by the FDA for the treatment of MM in combination with dexamethasone in patients who had received at

least 1 previous therapy. The recommended starting dose of LEN for patients with MM is 25 mg daily on days 1 to 21 of 28-day cycles (21/28). Recently, LEN 25 mg daily, using the 21/28 cycle, was approved by the FDA for the treatment of patients with MCL whose disease has relapsed or progressed after 2 previous therapies, one of which included bortezomib. The reported response rates and time to response to LEN demonstrate its utility, but definitions of response and results vary across the 3 indications and thus they are not compared herein.²⁻⁷

The safety profile for LEN across indications (del[5q] MDS, MM, and MCL) is similar, with neutropenia and thrombocytopenia being the most commonly reported treatment-related adverse events (AEs) in registration trials.²⁻⁷ It is not surprising that the most frequent AEs were hematologic in nature, because these are all hematologic malignancies. The most common nonhematologic AEs reported in the registration trials across indications included gastrointestinal disorders, fatigue, rash, pruritus, cough, pyrexia, dyspnea, peripheral edema, infection, insomnia, muscle cramps, tremor, and dizziness.²⁻⁷

Rash was a common AE in LEN registration trials, reported in up to a third of patients (Table 1),²⁻⁸ but was not generally cited as a

¹Department of Malignant Hematology, Moffitt Cancer Center, Tampa, FL

²Department of Medicine, Section of Hematology/Oncology, University of Arizona Cancer Center, Tucson, AZ

³Department of Medicine, Section of Hematology/Oncology, University of Chicago Medical Center, Chicago, IL

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Address for correspondence: Sara M. Tinsley, ARNP, AOCN, Department of Malignant Hematology, Moffitt Cancer Center, 12902 USF Magnolia Dr, Tampa, FL 33612

E-mail contact: sara.tinsley@moffitt.org

Table 1 Incidence of Rash in LEN Clinical Trials

Study	Patient Population	Patients Treated With LEN, n	Incidence of Rash		Incidence of Pruritus	
			All Grades, %	Grade 3/4, %	All Grades, %	Grade 3/4, %
MDS-003 ^{2,a}	IPSS low/Int-1-risk MDS with del5q	148	NR	6	NR	3
MDS-004 ^{5,7,b}						
LEN 5 mg	IPSS low/Int-1-risk MDS with del5q	69	30	NR	23	NR
LEN 10 mg	IPSS low/Int-1-risk MDS with del5q	69	20	NR	28	NR
MM-009 ^{3,8,a}	RRMM	177	33	<1	NR	NR
MM-010 ^{4,8,a}	RRMM	176	22	2	NR	NR
MCL-001 ^{6,b}	MCL relapsed or progressed after, or refractory to BORT	134	22	1	17	<1

Abbreviations: BORT = bortezomib; CTCAE = Common Terminology Criteria for Adverse Events; del5q = deletion of 5q; Int = intermediate; IPSS = International Prognostic Scoring System; LEN = lenalidomide; MCL = mantle cell lymphoma; MDS = myelodysplastic syndromes; MM = multiple myeloma; RRMM = relapsed/refractory multiple myeloma.

^aAdverse events in trial were graded according to the CTCAE version 2.

^bAdverse events in trial were graded according to the CTCAE version 3.

leading cause of treatment discontinuation (Table 2).²⁻⁷ The most common reasons for LEN dose modifications, treatment interruption, or permanent discontinuation of LEN were Grade ≥ 3 hematologic toxicities across all indications (Table 2).²⁻⁷ Pneumonia⁶ and thromboembolism³ were also reported as reasons for discontinuation of treatment. Surprisingly, postmarketing analysis of the Celgene Global Safety database in 2013⁹ showed that nonserious rash was the leading cause of early permanent discontinuation of LEN in the treatment of del(5q) MDS. Most discontinuations due to nonserious rash occurred within the first 8 weeks of LEN treatment. Because the median time to erythroid response in the MDS-003 study was 4.6 weeks with a range of 1 to 49 weeks,² this finding is concerning, because it suggests that patients treated with LEN for del(5q) MDS for < 8 to 12 weeks will be exposed to toxicity without a reasonable opportunity to achieve a response.¹⁰ Similar Global Safety Data for LEN in the treatment of MM and

MCL are not available, yet LEN-associated rash has been reported in the registration trials for these indications^{3,4,6} and likely poses a similar clinical dilemma.

Incidence of LEN-Associated Rash

Rash is a common AE in clinical trials using LEN. Although the overall incidence of any grade rash in LEN registration trials was 22% to 33%, more severe rash (Grade ≥ 3) was relatively uncommon, between < 1% and 6% (Table 1).²⁻⁷ Recently, a meta-analysis of LEN in clinical trials examined the incidence of LEN-associated rash.⁸ Ten trials with a total of 737 patients treated with 10 mg (n = 189) or 25 mg (n = 161) LEN monotherapy or 25 mg in combination with dexamethasone (n = 387) were included in the analysis. Diagnoses in these trials included non-del(5q) MDS, MM, chronic lymphocytic leukemia, myelofibrosis, T-cell lymphomas, and other non-Hodgkin lymphomas. LEN

Table 2 Lenalidomide Discontinuations and Dose Modifications Because of AEs in Clinical Trials

Study	D/C Due to AEs, %	D/C, Most Common AE (%)	D/C Due to Rash, %	Interruption/Reduction, %	Interruption/Reduction Most Common AE (%)	Interruption/Reduction Due to Rash, %
MDS-003 ^{2,a}	20	Thrombocytopenia or neutropenia (7)	3	NR/84	Thrombocytopenia and neutropenia (NR)	NR/NR
MDS-004 ^{5,7,b}						
LEN 5 mg	17	Neutropenia (1)	0	29/52	Neutropenia (12)/neutropenia (28)	4/NR
LEN 10 mg	9	Neutropenia (1)	0	46/55	Neutropenia (23)/neutropenia (33)	0/NR
MM-009 ^{3,a}	20	Thrombocytopenia or neutropenia (<5)	NR	77 ^c	NR/neutropenia and thrombocytopenia (NR)	NR/NR
MM-010 ^{4,a}	9 ^d	NR	NR	76 ^c	NR	NR/NR
MCL-001 ^{6,b}	19	Thrombocytopenia or neutropenia (NR)	NR	57/38	Thrombocytopenia and neutropenia (NR) ^e	NR/NR

Abbreviations: AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; D/C = discontinuation; LEN = lenalidomide; MCL = mantle cell lymphoma; MDS = myelodysplastic syndromes; MM = multiple myeloma.

^aAEs in trial were graded according to the CTCAE version 2.

^bAEs in trial were graded according to the CTCAE version 3.

^cInterruption and reduction reported as 1 value.

^dD/C reported for LEN and placebo groups.

^eThrombocytopenia and neutropenia were reported as the most common AEs leading to all LEN dose modifications.

Management of Lenalidomide Rash

treatment was significantly associated with an increased risk of all grade rash ($P < .001$).⁸ The overall incidence of rash with LEN treatment was 27.2% (191/716 patients for whom all grade rash data were available), with Grade ≥ 3 rash relatively uncommon at 3.6% (19/694 patients for whom Grade ≥ 3 rash data were available).⁸ Importantly, no difference in the incidence or severity of rash was reported according to dose of LEN or with LEN used in combination with dexamethasone.

Physiology of LEN-Related Rash

Drug-related dermatologic AEs are not uncommon.¹¹ Although classically attributed to anti-infectives and anticonvulsants, rashes develop after exposure to many different classes of medications, and range in severity from mild, localized, and short-lived to severe and life-threatening.¹¹⁻¹⁴ The specific pathophysiology of most drug-related skin reactions is unknown but is most often attributed to immunologic mechanisms or considered to be a direct result of chemical drug effects.¹¹ Immunologic reactions are typically independent of dose and often persist after discontinuation of the causative agent. Nonimmunologic reactions are dose-dependent¹⁵; their symptoms generally resolve soon after the causative drug has been stopped.

The typical presentations of drug-related skin reactions include varying rashes, erythema, and mucosal lesions.¹⁴ Such rashes are most commonly morbilliform or urticarial in nature.¹⁴ Less severe reactions are often accompanied by itching, whereas severe reactions are more likely to cause skin pain; still others are asymptomatic.¹⁶

Rash due to LEN exposure typically occurs within the first month of therapy and has been described as morbilliform, urticarial, dermatitis, acneiform, or undefined.¹⁷ Most LEN-related rash is mild to moderate^{2,3,5-8} and might present as patchy, raised, macular skin lesions on the trunk and proximal extremities, sometimes with localized urticaria, and occasionally associated with pruritus.^{6,8} Exfoliative skin lesions, vasculitis-like patterns, and severe reactions such as Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are less frequently reported with LEN.⁸

Knowledge of the reaction patterns and the temporal relationship between LEN initiation and rash onset is key in determining a causal link, because there are no available diagnostic or confirmatory tests to establish drug causation. A skin biopsy might be helpful if the patient has a blistering or pustular eruption,¹² but is often nonspecific and serves mainly to exclude other possible causes. Clinically, a skin biopsy can be especially useful in understanding the etiology of rash if cutaneous disease involvement is suspected.

The precise mechanism by which LEN causes skin toxicities is not understood. LEN appears to have direct and indirect effects, including the ability to inhibit cell growth and survival, induce apoptosis, inhibit adhesion to the host microenvironment, inhibit angiogenesis, and augment immune cell activity.¹⁸ It has been hypothesized that some or all of these effects might also influence keratinocytes in patients receiving LEN and contribute to rash development.⁸ As such, some authors attribute LEN-related rash to its direct antitumor effects, others to its indirect immunomodulatory effects. For example, LEN targets the ERK and phosphoinositide 3-kinase (PI3K)/Akt pathways in MM cells, interfering with cell growth and survival,¹⁸ and both pathways have been implicated in the development of rash with other agents.^{19,20} LEN also

potentiates immune-mediated cytotoxicity against MM cells,¹⁸ and severe skin reactions are generally T-cell-mediated.¹¹ Traditional immunoglobulin E-mediated hypersensitivity reactions underlying the development of urticarial rash have also been reported in select case reports of patients receiving LEN.^{21,22} Although the mechanism remains unclear, most LEN-related skin reactions do not require discontinuation of the drug.¹⁷

Grading Rash

Grading of rashes at least possibly related to treatment in clinical trials has been based on the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) grading criteria. Historically, grading of rash has been based on the percentage of body surface area involved with rash and implied an allergic reaction to an offending substance.²³ Yet, for many novel therapies known to have mechanisms of action that target elements of the skin, these criteria do not differentiate targeted effects of treatment from true traditional dermatologic AEs. The most recent edition of the common grading criteria, CTCAE version 4, reflects many of the changes proposed by an international multidisciplinary working group of clinicians and researchers.²⁴ The group was convened by the Multinational Association of Supportive Care in Cancer Skin Toxicity Study Group with the aim of incorporating more precise measures for grading dermatologic toxicities associated with targeted therapies into the CTCAE criteria.²³ Although the group focused primarily on rash associated with epidermal growth factor receptor inhibitors, a systematic review and categorization of the common terminology relative to dermatologic toxicities was conducted. Yet, registration trials of LEN for the treatment of MDS, MM, or MCL used previous versions of these criteria and, therefore, descriptions of rash severity are more ambiguous, less likely to adequately reflect the effect on quality of life, and do not provide precise measures for the incidence and severity of treatment-related dermatologic AEs.²³ Importantly, approved dosing, dose modifications, and drug discontinuation are driven by how these individual AEs are graded by clinicians involved in clinical trials. Thus, it is necessary to consider the specific version of these criteria in discussions or comparisons of frequencies or severity of dermatologic toxicities for any treatment, including LEN (Tables 1 and 2). In addition, clinicians must familiarize themselves with common dermatologic nomenclature for physical findings, to reduce the discordance in describing treatment-related AEs.

In January 2007, just over 1 year after the initial FDA approval of LEN for use in patients with transfusion-dependent anemia due to low- or intermediate-1-risk del(5q) MDS, an international group of MDS experts convened to discuss practical management of LEN in this population, including management of rash. The working group members suggested that rash most often resolved without interruption of therapy within 2 to 3 weeks.²⁵ Treatment recommendations included antihistamines, topical steroids, or a short course of low-dose oral prednisone. However, if these interventions are not effective and the rash progresses to Grade 4, LEN should be discontinued.¹

The Celgene Global Drug Safety database was searched for AEs spontaneously reported by health care practitioners or patients with MDS with postmarketing exposure to LEN between December 27, 2005 and June 13, 2013.⁹ Although cytopenias were the most commonly reported AEs, nonserious rash led to 72% of early

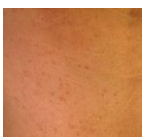
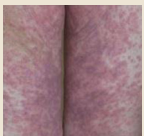
(within the first 2 months of treatment) permanent discontinuations of LEN. From a total of 36,793 AEs there were 2190 total rash AEs reported, of which 1593 had a reported action taken. Most rash cases were considered nonserious (91%; 1444/1593 cases). For rash AEs, dose modification was the most common intervention, reported in 591 (37%) cases, with no change in the dose reported in 545 (34%) cases and permanent LEN discontinuation in 457 (29%) cases.⁹ These data suggest discordance between assessment of rash severity and recommended interventions.

Sviggum and colleagues conducted an analysis of 75 patients with MM treated with LEN with or without dexamethasone and 23 patients with amyloidosis treated with LEN as a single agent.¹⁷ Interestingly, the incidence of rash with LEN treatment in patients with MM was the same with or without dexamethasone (7/24 patients [29%] and 15/51 patients [29%], respectively); rash AEs were most often seen in the first month of treatment and were most often described as mild with morbilliform or urticarial characteristics. Most patients did not require interruption of LEN treatment and rash often resolved spontaneously after a few days.¹⁷ For patients with moderate symptoms, LEN was temporarily withheld and reintroduced after

resolution of rash at a lower dose in most cases. Recurrent rash did occur in some cases, requiring a second interruption of therapy with subsequent resolution and reintroduction of LEN with additional dose reduction.¹⁷ Patients with amyloidosis in this analysis were more likely to develop rash and more likely to have moderate rash.

More severe rash associated with LEN, although rare, has been reported in the registration trials^{2,3,5-8} and in a recent peer-reviewed literature search including data from 1948 to 2013.²⁶ A total of 15 cases of either SJS (n = 13) or TEN (n = 2) were reported to be at least possibly related to LEN. The authors note the limitation in the literature analysis, because data were based most often on case reports characterized by variability in the grading of SJS and TEN, with most patients having exposure to multiple medications (including those with known strong associations with these cutaneous reactions), and a lack of confirmatory tissue analysis in many cases. This literature analysis emphasized the need to correctly and systematically establish causality of rash with use of consistent language in describing the severity of dermatologic AEs. Table 3 provides a summary of the grading of rash with the recommendations in the current prescribing information and those found in

Table 3 Identification and Management of LEN-Related Rash According to Grade

Grade	Example	Description (CTCAE) ^a	LEN Label Recommendations ^{1,27}	Published Recommendations
1		<10% of BSA 	No action recommended	Treat with topical corticosteroids and oral antihistamines until resolves ^{6,8,25}
2		10% to 30% of BSA 	Consider interruption or discontinuation	Treat with topical corticosteroids and oral antihistamines until resolves or Grade ≤1; consider dose interruption for intolerable Grade 2 rash ^{6,8,25}
3		>30% of BSA 	Consider interruption or discontinuation	Treat with oral antihistamines or oral corticosteroids until resolves or Grade ≤1; consider dose interruption ^{8,25}
4	Photo not available	Might have life-threatening consequences that require urgent intervention	Permanent discontinuation	No additional published recommendations
Stevens-Johnson Syndrome		<10% of BSA; separation of dermis	Permanent discontinuation	No additional published recommendations
Toxic Epidermal Necrolysis		>30% of BSA; separation of dermis	Permanent discontinuation	No additional published recommendations

Abbreviations: BSA = body surface area; CTCAE = Common Terminology Criteria for Adverse Events; LEN = lenalidomide.

^aBecause several distinct types of rash are designated within the CTCAE version 4, these descriptions have been generalized according to Grade.

Figure 1 Additional Examples of Grade 1 Lenalidomide (LEN)-Related Rash: Left Panels, 10 Days of Treatment With 10 mg LEN; Right Panel, 2 Weeks of Treatment With 10 mg LEN



10 days of treatment with 10 mg LEN

2 weeks of treatment with 10 mg LEN

more recent peer-reviewed literature^{1,6,8,27}; Figure 1 provides additional examples of Grade 1 rash.

Patient and Caregiver Self-Management

Setting expectations for patients and caregivers before the initiation of any cancer treatment is imperative to early identification of AEs. This allows for prompt intervention, which will reduce the severity of AEs and enable continuation of potentially effective therapies. Providing patients and their caregivers with descriptions (and photographs, when possible) of the possible dermatologic effects of LEN treatment, and explaining the mechanism of these changes, the difference in rash associated with LEN compared with allergic reactions that are associated with other drugs, when to contact the provider's office, and how to assess and manage the rash, will provide a framework for effective management of LEN. Setting expectations for the duration of LEN therapy, the expected time to response, and the strategies for management of rash, should it occur, will further engage patients and caregivers in self-management activities. Confirming the dose and schedule of administration for patients, particularly in patients requiring dose modifications, will promote adherence to the recommended treatment plan.

Conclusion

Lenalidomide provides an important treatment option for patients with MDS, MM, or MCL. The most common AEs in all registration trials were hematologic in nature and manageable with supportive care or dose modifications. Surprisingly, LEN-related rash, even though it was uncommon, was rarely moderate or severe, and rarely led to discontinuation in these trials, was reported as the most common reason for premature and permanent discontinuation of LEN in patients with MDS in a "real world" analysis. Because of the efficacy profile of LEN in treating these diseases, premature discontinuation limits the potential benefits to patients. Familiarity with the time to onset of LEN-related rash, common

physical findings, treatment strategies, and true indications for discontinuation of LEN is critical to maintaining treatment for patients who might benefit from LEN.

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