Case Report

Desensitization to Lenalidomide in a Patient With Relapsed Multiple Myeloma

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Clinical Practice Points

- Lenalidomide plus dexamethasone is a highly effective regimen that has significantly improved outcomes in patients with multiple myeloma (MM), and most patients with MM require therapy with lenalidomide at some point in their disease course. Although the drug is generally well tolerated, dermatologic reactions are not unusual and include a spectrum of manifestations, such as morbilliform, dermatitic, and acneiform eruptions; rarely severe reactions have been observed.
- IgE-mediated drug hypersensitivity reactions—such as urticaria and angioedema—carry the potential for more serious reactions with reexposure, and rapid desensitization protocols have been developed with reported success in patients with a history of IgE- or non–IgE-mediated hypersensitivity reactions.
- We report a patient with relapsed and refractory myeloma in whom urticaria developed when he was given lenalidomide and weekly dexamethasone for disease progression after stem cell transplantation; as a result, lenalidomide was discontinued. When the myeloma eventually progressed again, and after all other alternative therapies had been exhausted, the patient was hospitalized for rapid drug desensitization with lenalidomide.
- The rapid desensitization procedure consisted of an initial lenalidomide dose of 0.00025 mg, followed by increasing doses at decreasing time intervals until the target daily dose was reached 4.5 hours later. The only complication was hypertension, which antedated the desensitization effort. Lenalidomide with weekly dexamethasone was subsequently tolerated without further reactions for 4 months, until further myeloma progression occurred.
- This is the second successful report of lenalidomide desensitization and supports the utility of this technique when lenalidomide administration is essential for myeloma therapy after a hypersensitivity reaction.

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Introduction

Lenalidomide belongs to a class of immunomodulatory drugs that represents a promising advancement in the treatment of multiple myeloma (MM).[1-3] An oral structural analogue of thalidomide, lenalidomide was developed to produce an agent with a more favorable toxicity profile than that of its parent drug.[3,4] Initially approved in 2005 for the treatment of transfusion-dependent anemia caused by low- to intermediate-risk myelodysplastic syndromes with a 5q deletion, lenalidomide is also indicated for use with dexamethasone in patients with MM who are not responding to at least 1 previous therapy.[1,5]

Although thalidomide and lenalidomide share many similar mechanisms of action, lenalidomide is much more potent in its stimulation of T cells, production of interleukin-2 and interferon-γ, and inhibition of tumor neurosis factor-α.[4-6] Common adverse reactions of lenalidomide include fatigue, nausea, constipation, diarrhea, rash, increased risk of thromboembolism, and hematologic toxicities such as neutropenia and thrombocytopenia.[1,5,6]

The potential for dermatologic reactions is another common denominator between thalidomide and lenalidomide.[2,7-10] Such cutaneous reactions can range in severity from grade 1 to grade 4 rash with or without pruritus to manifestations of drug hypersensitivity, including case reports of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN).[2,8,11-13] Although not completely understood, at least 1 author has proposed an IgE-mediated cause for the development of a urticarial rash in a patient taking lenalidomide.[11]

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Multiple strategies have been used to address dermatologic reactions in patients undergoing treatment with lenalidomide and thalidomide including drug discontinuation, rechallenge at lower doses, pretreatment with antihistamines and corticosteroids, and drug desensitization.[7,9-11] Although limited literature exists on drug desensitization with either thalidomide or lenalidomide, desensitization has been used in the oncology setting and can salvage the use of critical agents in patients with few treatment alternatives.[7,11,14]

Case Report

Our patient was a 60-year-old man with IgG kappa and kappa light chain MM diagnosed in 2006. Initially, he received 4 cycles of VAD (vincristine/doxorubicin/dexamethasone), entered partial remission, and subsequently underwent high-dose cyclophosphamide mobilization and tandem autologous stem cell transplantation in October 2007 and April 2008 using high-dose melphalan conditioning. He then remained stable until July 2010 when his disease progressed; oral dexamethasone 40 mg once weekly and lenalidomide 25 mg daily for the first 21 days in a 28-day cycle were commenced.

On the fifth day of lenalidomide therapy, he reported the development of a rash in the form of hives and pruritus. He stated the reaction was primarily limited to his arms and hairline and that the rash appeared for 30 minutes before spontaneously disappearing, although the pruritus persisted. A physical examination performed by his primary care physician the following day was unremarkable, with no maculopapular or other type of rash detected. He denied fever or lymphadenopathy but continued to experience pruritus. At that point, lenalidomide was discontinued by his physicians. However because of his concern about his myeloma, the patient started taking it again of his own accord and reported worsening pruritus as well as another outbreak of hives, which were more extensive than previously but which subsided after several hours. He and his family members consistently described the rash as urticarial, without a morbilliform or maculopapular component.

Because of concern that this rash could represent an IgE-mediated reaction to lenalidomide, the patient was switched to a regimen of weekly cyclophosphamide and continued on weekly dexamethasone. After an initial response, bortezomib was added in March 2011 because of an increasing monoclonal protein level. However he required hospitalization in April 2011 for renal insufficiency secondary to further disease progression. His past medical history was significant for type 2 diabetes mellitus (treated with metformin and insulin), hypertension, and compression fractures. Additional medications at the time of admission included dexamethasone 40 mg/wk, along with ranitidine, fosinopril, acyclovir, pamidronate, granisetron, docusate, and oxycodone as needed. His fosinopril was held and later replaced with amlodipine because of compromised renal function and increased potassium levels (5.9 mmol/L). Metformin and acyclovir were also held.

During his hospital course, the decision was made to restart lenalidomide along with weekly dexamethasone because his other therapeutic options at this point were limited. Based on the concern that a more serious hypersensitivity reaction could be precipitated by further exposure to lenalidomide, it was recommended that the patient, who had no additional history of drug or other allergies, be rapidly desensitized to this drug rather than rechallenged with a lower dose. Moreover, the target dose of lenalidomide needed to be reduced to 10 mg daily, as recommended by the manufacturer for patients with compromised renal function.

An inpatient oral desensitization protocol was developed based on the case report by Phillips et al[11] and performed under the University Health Network (UHN) Procedure for Initiating Drug Desensitization. The procedure was in accordance with the Declaration of Helsinki. No concomitant antihistamines or immediate pretreatment corticosteroids were administered. The contents of 3 lenalidomide 10-mg capsules were diluted with normal saline to produce 3 different suspensions with concentrations of 0.0025, 0.025, and 1 mg/mL, respectively. Because the capsule contents failed to dissolve initially, it was continuously agitated during preparation to ensure proper dispersion and complete dissolution of the active agent. Escalating doses of each concentration were then administered at decreasing time intervals, culminating in a final administration of the target maintenance dose of 10 mg (Table 1).

During desensitization, the patient received a total of 20.25 mg of lenalidomide in an attempt to induce tolerance to 10 mg daily. In comparison, Phillips et al[11] used 25.205 mg during desensitization to achieve a maintenance dose of 15 mg. The entire procedure took 4.5 hours, during which UHN Standard Orders for Patient Monitoring During Drug Desensitization were followed. The only adverse reaction experienced by the patient was elevated blood pressure that required intervention with metoprolol and nitroglycerin at 2 separate junctures (Table 1). However the patient had had uncontrolled hypertension since admission; his baseline pressure the morning of desensitization was 190/86 mm Hg, and with appropriate pharmacologic management the desensitization schedule was able to continue without any additional problems.

The next day, the patient was started on lenalidomide 10 mg daily. He continued to experience uncontrolled hypertension while an inpatient despite doubling his amlodipine dose and initiating twice-daily metoprolol. His hospital course after desensitization was further complicated by the development of group B streptococcal right-sided pneumonitis and hematuria of uncertain cause. Despite these issues, the patient was able to be discharged in satisfactory condition 8 days after lenalidomide desensitization at the planned dose of 10 mg daily for the remainder of the 21-day portion of the 28-day cycle. He continued on lenalidomide for 4 months, with stable disease before further disease progression was noted.

Discussion

Drug hypersensitivity is a complex phenomenon with multiple mechanisms that are not yet completely understood.[15] The discrepant terminology used to describe hypersensitivity, allergic and nonallergic reactions, and their respective pathways further compounds the issue.[15-17] Although some limit an allergy to IgE-mediated reactions, others broaden the term to include any drug reaction with an immune-mediated component.[15,17] Hypersensitivity has also been used to describe both immune- and non–immune-mediated mechanisms.[15,17] There does appear to be agreement, however, that drug hypersensitivity to an agent triggers a reproducible reaction that is not experienced by a person who is not hypersensitive.[14,15,17]

Cutaneous reactions are commonly reported manifestations of multiple types of drug hypersensitivity.[14,15] As such, the possibility

Table 1 Oral Lenalidomide Desensitization Schedule Administered to Patient over Time[a]

Time	Concentration (mg/mL)	Dose (mL)	BP (mm Hg)	Pulse (BMP)	RR (BPM)	Temp. (°C)	O_2 Sat. (%)	Intervention
6:00 AM		–	170/80	72	18	36.2	96	None
10:00 AM		–	190/86	90	18	36.1	98	None
12:25	0.0025	0.10	170/70	90	18	36.0	99	None
13:30		0.50	174/78	94	18	35.9	99	None
14:05	0.025	0.10	196/94	100	18	36.2	97	Metoprolol 50 mg
14:25		0.50	184/88	98	18	36.0	98	None
14:45		1.00	–	–	–	–	–	None
3:00 PM		3.00	206/94	80	18	35.9	97	Nitroglycerin 0.6-mg patch
15:15		5.00	178/90	90	18	36.0	99	None
15:30	1.00	0.25	182/90	94	18	36.0	99	None
15:45		0.50	178/86	80	18	36.1	99	None
4:00 PM		0.75	162/70	70	18	36.2	99	None
16:15		1.00	156/62	70	18	36.0	98	None
16:30		2.50	156/80	76	18	36.0	99	None
16:45		5.00	154/76	72	18	36.0	98	None
5:00 PM		10.0	160/80	76	18	36.1	99	None
6:00 PM			160/76	80	18	36.1	99	None
20:30			166/66	96	18	36.9	96	None
10:00 PM			162/68	98	18	36.7	97	None

Abbreviations: BMP = beats per minute; BP = blood pressure; BPM = breaths per minute; O_2 Sat. = oxygen saturation; RR = respiratory rate; Temp. = temperature.
[a] Incremental increase in dose was provided and vital organs were monitored during the process. Appropriate medical interventions used to maintain stability.

of hypersensitivity must be carefully and clinically considered in all patients presenting with rash, especially with agents associated with severe reactions like SJS and TEN that require immediate intervention.[14] The temporal relationship between initiation of the drug and the onset of the adverse reaction is a key factor in evaluating the causative link of a hypersensitivity reaction; presentation typically ranges between 1 week and 1 month.[14] Several tests also exist to aid in the identification of a suspected hypersensitivity reaction, including skin tests, patch tests, and provocation tests.[14,15] Unfortunately, definitive confirmation with testing is difficult, and diagnosis is still largely based on the clinical judgment of the practitioner.[14]

Although some rashes from lenalidomide have been managed with simpler measures such as dose reduction, antihistamines, and corticosteroids,[18] in this case, it was determined that the patient's reaction constituted a drug hypersensitivity—possibly IgE-mediated, which warranted discontinuation of lenalidomide until other treatment options had been exhausted. Tolerance was induced by systematically reintroducing small amounts of lenalidomide into the patient at frequent intervals, culminating with the full therapeutic dose of lenalidomide per the usual 21-day schedule. Ideally, daily administration of the culprit drug follows desensitization if repeated exposure is planned. Such a strategy has been successful after penicillin and aspirin desensitization, as tolerance is lost within hours or days.[19] However lenalidomide funding limitations in Ontario did not allow continuous administration; moreover, the serum concentration of lenalidomide is zero by 24 hours after administration. Despite these limitations, urticaria did not recur and repeated desensitization before subsequent cycles was not necessary, in contrast to the management of hypersensitivity reactions to other antineoplastic agents administered on an interval schedule.[20]

Benefits of drug desensitization protocols such as this one have been demonstrated in IgE and non-IgE immunologic reactions, as well as some non–immune-mediated reactions.[16,17] The mechanisms are not yet fully understood, and the pathways behind desensitization in non-IgE and nonimmune reactions are even less clear. Despite this limited knowledge, desensitization has still proved to offer a potential solution for many patients when treatment alternatives are limited and the benefits of desensitization outweigh the risks.[16] At the same time, it should be noted that desensitization is an evolving practice, and the incomplete understanding of the mechanisms behind it means current protocols are founded on the success and failure of previous clinical experiences.[14]

Conclusion

Lenalidomide is a promising pharmaceutical agent effective in several hematologic conditions. Its favorable results in MM have led to its use as first-line and maintenance therapy in selected patients. With this increasing use comes a more pressing need to properly identify and manage treatment-related dermatologic reactions. To the best of our knowledge, this is only the second report of an attempt at oral desensitization with lenalidomide. The patient's ability to tolerate resumption of lenalidomide without development of rash or

pruritus after undergoing rapid desensitization, complicated only by elevated blood pressure that may or may not have been related to the procedure, should be deemed a success. Although future controlled studies are needed, the combination of these reports with a successful desensitization suggests a safe and effective option for patients who experience certain types of rash with lenalidomide administration.

Disclosures

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