Lusíadas Scientific Journal • VOL. 3 • #2 • abril/junho 2022

Desensitization in a Delayed Hypersensitivity Reaction to Lenalidomide

Dessensibilização numa Reação de Hipersensibilidade Tardia a Lenalidomida

Daniela Brandão Abreu [1], Josefina Rodrigues Cernadas [1,2]*

***Corresponding Author**/Autor Correspondente
Daniela Brandão Abreu, MD [danielabrandaoabreu@gmail.com]
Serviço de Imunoalergologia, Centro Hospitalar Universitário de São João, Porto, Portugal
Alameda Prof. Hernâni Monteiro, 4200-319 Porto, Portugal
ORCID iD: Daniela Brandão Abreu https://orcid.org/0000-0001-7369-3723

doi: 10.48687/lsj.104

Resumo

A lenalidomida é um fármaco utilizado no tratamento de neoplasias hematológicas, com reações de hipersensibilidade descritas na literatura. Os protocolos de dessensibilização a lenalidomida estão pouco descritos e não estão estabelecidos. Assim, fazemos alusão ao caso clínico de um doente do sexo masculino, 70 anos, sob ciclos mensais de lenalidomida, referenciado ao serviço de Imunoalergologia por aparecimento de exantema maculopapular generalizado no 16º dia do terceiro ciclo de tratamento.

A resolução das lesões verificou-se duas semanas após terapêutica com corticosteroide sistémico e tópico. Após avaliação do risco-benefício, foi elaborado um protocolo de dessensibilização lenta, que o doente tolerou, embora tenha tido necessidade de diminuição da dose diária após terminar o protocolo, dado o reaparecimento do exantema e a possibilidade de o mesmo ser dose-dependente.

A descrição e publicação de casos com procedimentos de dessensibilização em reações tardias é especialmente relevante, nos casos em que são descritas reações de hipersensibilidade T-mediadas, bem como mecanismos dose-dependentes.

Palavras-chave: Dessensibilização Imunológica; Exantema; Hipersensibilidade a Fármacos; Hipersensibilidade Tardia; Lenalidomida/efeitos adversos

Abstract

Lenalidomide is an immunomodulator analog of thalidomide used in the treatment of hematologic malignancies, both with previous reports of hypersensitivity reactions. Desensitization protocols with lenalidomide are not established and few are published. Therefore, we describe a clinical case of a 70-year-old male patient under monthly cycles of lenalidomide referred to our Allergy department due to generalized maculopapular exanthema appearing on the 16th day of the third cycle of treatment.

After treatment with systemic and topical corticosteroid for 1 week, resolution of all lesions was present on the following 2 weeks. A slow desensitization protocol was performed after a risk-benefit assessment, with tolerance, although dose reduction was necessary, given exanthema re-appearance, which seemed to be dose-dependent.

1. Serviço de Imunoalergologia, Centro Hospitalar Universitário São João, Porto, Portugal. **2.** Unidade de Imunoalergologia, Hospital Lusíadas, Porto, Portugal.
Recebido/Received: 29/03/2022 – **Aceite/Accepted:** 19/05/2022 – **Publicado online/Published online:** 30/06/2022 – **Publicado/Published:** 30/06/2022

Description and publication of cases with desensitization procedures in late reactions is relevant, especially in cases where T-mediated hypersensitivity reactions, as well as dose-dependent mechanisms, are described.

Keywords: Desensitization, Immunologic; Drug Hypersensitivity; Exanthema; Hypersensitivity, Delayed; Lenalidomide/adverse effects

Introduction

Lenalidomide is an immunomodulatory analog of thalidomide used in the treatment of multiple myeloma, myelodysplastic syndromes, and amyloidosis.[1] Adverse reactions related to lenalidomide include myelosuppression (mainly neutropenia but also thrombocytopenia), gastrointestinal problems, skin eruption, atrial fibrillation, asthenia, and decreased peripheral blood stem cell.[2] The prevalence of hypersensitivity reactions to lenalidomide varies from 6% to 43%, with morbilliform, urticarial and maculopapular rashes being mostly described, frequently in the first month of therapy.[3] Skin immunologic reactions are typically dose-independent and often persist after discontinuation of the causative agent, whereas nonimmunologic rashes are dose-dependent and their symptoms generally resolve soon after the causative drug has been stopped.[4] About 30% of these are late reactions, whose mechanisms are not well understood.[1] Desensitization protocols, with this drug, are not established and few are published. Thus, we describe a clinical case of a long desensitization protocol to lenalidomide in a patient with multiple myeloma and a concomitant delayed hypersensitivity reaction.

Case Report

A 70-year-old male patient diagnosed with multiple myeloma under lenalidomide (10 mg/day on days 1 to 21 of a 28-day cycle) since January 2021, was referred to our Allergy department due to generalized pruritic maculopapular exanthema appearing on the 16th day of the third cycle of treatment, lasting two weeks, and worsening (Fig. 1).

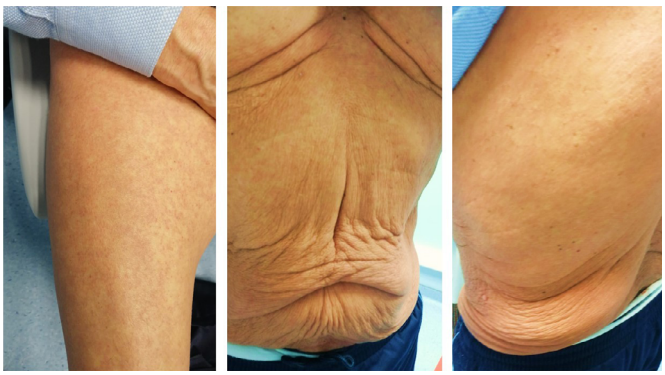

Figure 1. Skin lesions appearing on the 16th day of the third cycle of treatment with lenalidomide.

Topical betamethasone and oral prednisolone were prescribed with a slow tapering regimen for 3 weeks. The patient was significantly better on the 7th day, with resolution of all lesions on the following 2 weeks. The patient never presented other symptoms or signs of systemic involvement and no peripheral eosinophilia neither other laboratory abnormalities, such as liver and kidney disturbances, were found.

In the absence of a therapeutic alternative and after a risk--benefit assessment with the hematologist, a slow desensitization protocol was organized, over 21 days, with a target dose of 10 mg/day, starting at 1/100 of the cumulative dose as an oral suspension prepared in the hospital pharmacy, once daily, with increasing dose, on average, every 2-3 days (Table 1). The patient was monitored for cutaneous lesions and laboratory abnormalities, once a week, during all process. No skin tests neither other diagnostic workup was performed before the desensitization protocol, as it was imperative to restart the drug as soon as possible. An informed consent was signed by the patient at the beginning of the protocol.

Table 1. Desensitization protocol to lenalidomide.

Day	Dose (mg)
1	0.1
2	0.1
3	0.3
4	0.3
5	0.6
6	0.6
7	1.2
8	1.2
9	2.4
10	2.4
11	2.4
12	4.8
13	4.8
14	4.8
15	4.8
16	4.8
17	4.8
18	7
19	7
20	7
21	10

The protocol was completed with success and the patient was on daily medication, until the appearance of a generalized maculopapular exanthema 15 days after finishing the desensitization process (Fig. 2). During this period, the patient was still under 10 mg of lenalidomide every day.

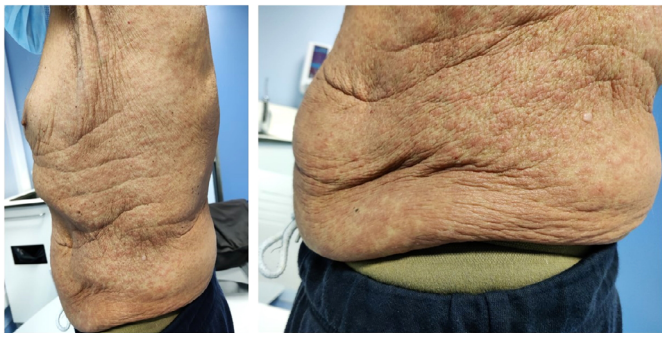

Figure 2. Skin lesions appearing 15 days after finishing the desensitization process with lenalidomide.

At this stage, no laboratory abnormalities neither fever was reported, although the patient required topical corticosteroid, as well as systemic with tapered reduction, with resolution of the skin lesions in two weeks. This reaction led to the discussion with the hematologist, since there are literature reports of delayed-type reactions dose-dependent, whose immunologic mechanism is not well understood.[4,5] As lenalidomide efficacy for treatment of multiple myeloma is established until a minimum of 5 mg/day, we have discussed the option of daily dose reduction with the assistant hematologist. Therefore, one week after skin lesions resolved, patient restarted lenalidomide treatment with a daily posology of 7.5 mg and no need for a desensitization protocol. Since then, patient has maintained continuous treatment with 7.5 mg lenalidomide per day, without stopping and with no complications to date.

Discussion

Most lenalidomide-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.[2] The precise mechanism by which lenalidomide causes skin reactions is not understood but appears to involve direct antitumor effects, as well as indirect immunomodulatory effects.[1,4] Lenalidomide inhibits cell growth and survival, induces apoptosis, inhibits adhesion to the host microenvironment and angiogenesis, augments immune cell activity, and affects keratinocytes' function.[1] Indeed, both mechanisms could be present in the same patient, as a case report of a 78-year-old man presenting with an erythematous maculopapular exanthema on the second cycle of lenalidomide and with positive skin patch test to lenalidomide 10% in dimethyl sulfoxide, also requiring daily dose reduction to maintain tolerance.[5] On the other hand, there is evidence that dose reduction may not be sufficient to establish tolerance.[2] Our patient did not perform skin tests to confirm a T-mediated hypersensitivity, since there was an imperative need to restart the treatment and because skin tests to lenalidomide are not standardized. However, skin lesions appearance after completion of the desensitization protocol was reproducible, in terms of timing and appearance to the index reaction. Moreover, the index reaction only occurred at the third cycle, demonstrating in some way a process of allergic sensitization.

As a conclusion, drug desensitization protocols allow patients with immediate hypersensitivity reactions to safely comply with establish treatment. However, in non-immediate hypersensitivity reactions, protocols are not standardized for most drugs. For example, there are literature reports of desensitization protocols for lenalidomide late-hypersensitivity reactions using corticosteroids during the process, whereas our patient only used steroid treatment for the management of skin reactions.[2] The authors believe that any grade lenalidomide-related rash should be appropriately managed through awareness of symptoms, appropriate and prompt intervention, with performance of desensitization protocols after a risk-benefit assessment. On the other hand, given the scarcity of published protocols in delayed-type reactions, every attempt should be shared with the medical community, so the authors believe that description and publication of cases with desensitization procedures in late reactions is relevant.

Responsabilidades Éticas

Conflitos de Interesse: Os autores declaram a inexistência de conflitos de interesse na realização do presente trabalho.

Fontes de Financiamento: Não existiram fontes externas de financiamento para a realização deste artigo.

Confidencialidade dos Dados: Os autores declaram ter seguido os protocolos da sua instituição acerca da publicação dos dados de doentes.

Consentimento: Consentimento do doente para publicação obtido.

Proveniência e Revisão por Pares: Não comissionado; revisão externa por pares.

Ethical Disclosures

Conflicts of Interest: The authors have no conflicts of interest to declare.

Financing Support: This work has not received any contribution, grant or scholarship.

Confidentiality of Data: The authors declare that they have followed the protocols of their work center on the publication of data from patients.

Patient Consent: Consent for publication was obtained.

Provenance and Peer Review: Not commissioned; externally peer reviewed.

Contributorship Statement

DA and JC: Writing, content review and final approval

Declaração de Contribuição

DA e JC: Escrita, revisão do conteúdo e aprovação final

References

1. Imbesi S, Allegra A, Calapai G, Musolino C, Gangemi S. Cutaneous adverse reactions to lenalidomide. Allergol Immunopathol. 2015;43:88-91. doi: 10.1016/j.aller.2013.07.005.
2. Sviggum HP, Davis MD, Rajkumar SV, Dispenzieri A. Dermatologic adverse effects of lenalidomide therapy for amyloidosis and multiple myeloma. Arch Dermatol. 2006;142:1298-302. doi: 10.1001/archderm.142.10.1298.
3. Patrizi A, Venturi M, Dika E, Maibach H, Tacchetti P, Brandi G. Cutaneous adverse reactions linked to targeted anticancer therapies bortezomib and lenalidomide for multiple myeloma: new drugs, old side effects. Cutan Ocul Toxicol. 2014;33:1-6. doi: 10.3109/15569527.2013.787086.
4. Tinsley SM, Kurtin SE, Ridgeway JA. Practical management of lenalidomide--related rash. Clin Lymphoma Myeloma Leuk. 2015;15 Suppl:S64-69. doi: 10.1016/j.clml.2015.02.008.
5. Noguerado-Mellado B, Rojas-Pérez-Ezquerra PD, Tornero Molina P, Ballesteros M, Zubeldia Ortuño JM. Delayed hypersensitivity reaction to lenalidomide: 2 different clinical patterns in the same patient. J Investig Allergol Clin Immunol. 2019;29:309-11. doi: 10.18176/jiaci.0386.