Pomalidomide desensitization in a patient hypersensitive to immunomodulating agents

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ABSTRACT
Despite progressive treatments with tandem stem-cell transplantation, patients with incurable myeloma eventually succumb to relapsed or refractory disease if left untreated. Promising agents such as proteasome inhibitors and immunomodulating imide drugs (imids), including the newer-generation agent pomalidomide, in combination with lower-dose dexamethasone, have been shown to be effective and to significantly improve and prolong survival in pretreated patients.

Although the incidence of pomalidomide hypersensitivity reaction (hsr) in this class of drugs is not as well known, we have documented cutaneous toxicity (grade 3 by the Common Terminology Criteria for Adverse Events, version 4) in 2 separate cases (not yet published). Because the imids are chemically, structurally, and pharmacologically similar, it is not unreasonable to consider possible cross-reactivity in pomalidomide recipients who developed hsr when receiving previous lines of imids. As a patient’s advocate, it is only prudent to provide a responsible, and yet practical, means to better address cross-sensitivity for patients.

Intervention with the use of a rapid desensitization program (rdp) as a preventive measure should be introduced before initiating pomalidomide. Such a proactive measure for the patient’s safety will ensure a smooth transition into pomalidomide treatment. A hsr can be either related or non-related to immunoglobulin E. As imids become an essential treatment backbone for myeloma and other plasma-cell diseases, an increasing number of patients could experience skin and other life-threatening toxicities, resulting in unnecessary discontinuation of these life-prolonging agents. An extemporaneously prepared pomalidomide suspension developed at our centre enables patients to undergo rdp safely. Patients enjoy a good quality of life and clinical response after the rdp procedure.

Key Words  Desensitization, hypersensitivity reactions, immunomodulating agents

INTRODUCTION
Plasma-cell diseases, including multiple myeloma and amyloidosis, are considered incurable, and patients typically relapse at some point despite the evolution of more effective frontline treatment strategies. Lenalidomide and pomalidomide are newer-generation immunomodulating imide drugs (imids) approved as additional therapeutic options when prior treatments have failed. These orally administered derivatives of thalidomide are chemically structured to improve efficacy and safety. Lenalidomide is used in combination with other chemotherapy agents and as maintenance until relapse after autologous stem-cell transplantation. Importantly, lenalidomide and dexamethasone have become the backbone of the next generation of highly effective combination regimens when administered with carfilzomib, ixazomib, or monoclonal antibodies.

Pomalidomide is a particularly potent imid, with studies in relapsed patients having demonstrated efficacy for those in whom both bortezomib- and lenalidomide-containing regimens have failed or were intolerable, and for those with documented disease progression on the preceding regimen. Although belonging to the same family of drugs, pomalidomide has incomplete cross-resistance with lenalidomide in terms of anti-myeloma effect. Not surprisingly, pomalidomide and dexamethasone are also being used in combination with carfilzomib, ixazomib, and monoclonal antibodies such as elotuzumab and daratumumab in people for whom prior lenalidomide has failed. The key role played by the imids in the management of myeloma cannot, therefore, be underestimated.

A hypersensitivity reaction (hsr) manifested by dermatologic eruptions secondary to an imid is often problematic, resulting in the withholding of critically needed treatment in advanced disease. The observed rates of hsr...
in clinical trials are limited, having been reported to range between 1% or greater and less than 5%. Of 35 patients, 1 (2.9%) withdrew from a study of pomalidomide plus low-dose dexamethasone because of skin rash, and of 38 patients, 1 (2.6%) was suspected of a grade 2 skin rash in a separate phase 1 maximal tolerated dose study of pomalidomide. But those reports might not reflect rates observed in clinical practice, given that the eligibility criteria clearly excluded patients with a prior history of drug hypersensitivity to lenalidomide or thalidomide.

Benefits of drug desensitization protocols have been demonstrated in immunologic reactions related to immunoglobulin E, as well as in some non–immunoglobulin E immune-mediated reactions. Such protocols have proved to offer a potential solution for many patients when treatment alternatives are limited and the benefits of desensitization outweigh the risks. Principles and protocols for rapid drug desensitization have been described and used with success for patients with grade 1 or 2 skin rash, and of 1 (2.9%) withdrew from a study of pomalidomide plus low-dose dexamethasone because of skin rash, and of 38 patients, 1 (2.6%) was suspected of a grade 2 skin rash in a separate phase 1 maximal tolerated dose study of pomalidomide. But those reports might not reflect rates observed in clinical practice, given that the eligibility criteria clearly excluded patients with a prior history of drug hypersensitivity to lenalidomide or thalidomide.

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**CASE DESCRIPTION**

**Medical History and Treatments**

In 2004, a 54-year-old woman was diagnosed, by fluorescence in situ hybridization, with immunoglobulin G lambda multiple myeloma with del 13q. Despite a strong family history of rheumatoid arthritis, the patient was not diagnosed with that disease. She did not have asthma, and she had no food or medication allergies to report.

Thalidomide was initiated as maintenance after upfront tandem autologous stem-cell transplantation, but its use was complicated by the development of significant hives and generalized rash (grade 3 by the Common Terminology Criteria for Adverse Events, version 4), which required its cessation about a week and a half after the start of the 1st cycle of treatment. At the time of the thalidomide hsr, the patient was taking multivitamins and minerals, and vitamin D and calcium supplements, with the occasional use of acetaminophen for pain. She remained in partial remission for 55 months after her autologous stem-cell transplantation.

When the patient’s monoclonal protein spiked to 28 g/L, lenalidomide was considered to be the next-best treatment option. Because a cross-sensitivity risk with thalidomide was probable, a lower dose was tried in the 1st cycle of treatment. However, within a few days, the patient experienced a recurrence of the dermatologic reaction, characterized again by hives (grade 3) and intense itchiness over her scalp, which spread to her groin and arms on 7 June 2011. She had been maintained on other medications without the occurrence of adverse events: oral penicillin 300 mg daily (continuous prevention for a previous encapsulated bacterial infection), ranitidine, famciclovir (recent herpes infection), oral dexamethasone 12 mg weekly (part of her chemotherapy regimen), and oral aspirin 81 mg daily (for thrombosis prevention while on an immunomodulating agent).

Lenalidomide was discontinued, and on 31 August 2011, the patient commenced weekly oral cyclophosphamide and dexamethasone instead. That combination treatment was discontinued in November 2013 because of myeloma progression. During the next 17 months, the patient received multiple chemotherapies: bortezomib-based therapy, and trametinib plus an Akt inhibitor, followed by selinexor (KPT-330) plus dexamethasone, both on clinical trial, without a durable response. In desperation, D-PACE (dexamethasone plus cisplatin–doxorubicin–cyclophosphamide–etoposide) was administered for 1 cycle, but her course was complicated by significant infections and chemotherapy-related toxicity; further cycles were felt to be excessively risky.

Given that this patient had not experienced an adequate trial of the mib family of drugs because of her well-documented hsr to thalidomide and lenalidomide (as already described), there was concern about a potential intolerance to pomalidomide. The team decision was then to attempt a rdp for pomalidomide to offset the anticipated cross-sensitivity to the mibs that had already been tried.

During the protocol, the patient denied any adverse events and experienced only minor fluctuations of her systolic blood pressure, and those only at the first few steps of the procedure. An intravenous line infusing normal saline was maintained to keep a vein open. The patient’s overnight hospitalization was uneventful, and the next morning, she was rechallenged with the target dose and discharged about 4 hours later without any adverse reaction.

**RDP Method**

After informed consent had been obtained from the patient and all questions about potential risks and benefits were answered, her clinical history was assessed. On the day scheduled for the rdp, 3 mg capsules of pomalidomide (Pomalyst: Celgene, Mississauga, ON) were suspended in 0.5% carboxymethylcellulose sodium usp (Sigma–Aldrich, Oakville ON); 0.5 mL food-grade 0.25% Tween 80 (Sigma–Aldrich) was admixed to facilitate serial dilutions for use in the preparation of dosing syringes for the desensitization. Literature search results supported the idea that carboxymethylcellulose could be used to suspend pomalidomide in solution in murine model. We also took the liberty of adding the food-grade polysorbate (Tween 80), a non-ionic surfactant and emulsifier, to the suspension. Together, the lipophilic and hydrophilic properties of the polysorbate enabled aqueous suspension of the pomalidomide to achieve stability.

Per our hospital policy, an anaphylaxis kit was available at the patient’s bedside. A total of 10 syringes preloaded with increasing concentrations of the suspension were administered orally stepwise (Table 1). After each oral dose, the patient was asked to take a mouthful of water to and swish and swallow as a chaser. On average, 15–20 minutes...
TABLE I Drug concentrations given and vitals monitored during the patient’s rapid desensitization program (RDP)

| RDP step | Concentration of stock solution (mg/mL) | Dose (mg) | Administration Oral amount (mL) | Time of dose | Blood pressure (mmHg) | Heart rate | Respiration rate | Temperature (°C) | O₂ saturation (%) |
|----------|----------------------------------------|-----------|-------------------------------|-------------|----------------------|-----------|-----------------|-----------------|------------------|
| 1        | Solution D (0.001 mg/mL)               | 0.00025   | 0.25                          | 11h50       | 118/80               | 89        | 18              | 36.4            | 99               |
| 2        | Solution B (0.01 mg/mL)                | 0.00125   | 1.25                          | 12h05       | 118/79               | 93        | 18              | 36.7            | 99               |
| 3        | Solution C (0.01 mg/mL)                | 0.0025    | 2.5                           | 12h20       | 121/81               | 89        | 18              | 36.4            | 99               |
| 4        | Solution D (0.01 mg/mL)                | 0.0125    | 1.25                          | 12h35       | 127/82               | 87        | 18              | 36.6            | 99               |
| 5        | Solution B (0.1 mg/mL)                 | 0.025     | 2.5                           | 12h50       | 115/79               | 88        | 18              | 36.6            | 105              |
| 6        | Solution B (0.1 mg/mL)                 | 0.125     | 1.25                          | 13h05       | 119/80               | 87        | 18              | 36.6            | 99               |
| 7        | Solution B (0.1 mg/mL)                 | 0.25      | 2.5                           | 13h20       | 130/81               | 85        | 18              | 36.6            | 103              |
| 8        | Solution B (0.1 mg/mL)                 | 0.25      | 2.5                           | 13h20       | 130/81               | 85        | 18              | 36.6            | 103              |
| 9        | Solution A (1 mg/mL)                   | 0.75      | 0.75                          | 13h50       | 117/82               | 88        | 18              | 36.6            | 105              |
| 10       | Solution A (1 mg/mL)                   | 1         | 1                             | 14h05       | 135/85               | 89        | 18              | 36.7            | 105              |
| Post-RDP |                                        |           |                               | 23h30       | 110/72               | 89        | 18              | 37.5            | 98               |
|          |                                        |           |                               | 06h20       | 105/68               | 84        | 18              | 37.5            | 97               |

Elapsed between each step, with continuous monitoring of vitals. The desensitization process took approximately 3.5 hours to complete. The patient made no complaint of any obvious toxicity or recurrence of hSR during the RDP.

**DISCUSSION**

Angioedema and urticaria have been reported with use of thalidomide, including during the post-marketing experience with pomalidomide. The product monograph for Pomalyst states that patients with a prior history of allergic reactions related to thalidomide or lenalidomide were excluded from the pomalidomide clinical studies and could be at increased risk for hypersensitivity. The use of Pomalyst is therefore contraindicated in those patients. Although nonimmune mechanisms could account for the reactions to Pomalyst, the assumption has been that they do represent hypersensitivity phenomena, and there is concern that the similarity in chemical structure and pharmacologic action of the various thalidomide might lead to cross-reactivity for all drugs in the class. In myeloma therapy, the antiproliferative activities of thalidomide, lenalidomide, and pomalidomide are linked to cereblon expression as a target and to molecular or structural affinity. Lenalidomide and pomalidomide are derivatives of thalidomide, which explains their similarities in chemical configuration. Lenalidomide was developed by the addition of an amino group (NH₂) at the 4th position of the phthaloyl ring and removal of the carbonyl group (C=O) at the 4-amino-substituted phthaloyl ring position. For pomalidomide, both of those functional groups were deemed essential in their respective positions. The structural similarities of the three molecules can be viewed in a report from Fischer et al.

Given the theoretical possibility of cross-sensitivity between the thalidomide, patients have been prevented from receiving further treatments such as pomalidomide. On the one hand, the strong argument against the inclusion of patients with prior thalidomide into the pomalidomide clinical trials was a valid concern, but on the other hand, finding a clinical solution that circumvents the problem could be equally important. The need to be eligible for further treatments could very well have served as a counterargument in support of patients adversely affected during prior treatments with both thalidomide and lenalidomide, provided that a RDP was in place. That need for eligibility in fact constituted a supportive statement for the use of RDP as a safety net in this patient cohort. Only with the use of a desensitizing process can continuity in offering treatments be ensured for patients in need, with concurrent attention to patient safety.

We were obviously unable to determine whether, because of the potential for cross sensitivity, pomalidomide administration would have been safe in this patient without first using desensitization. However, according to the principle of non-maleficence (Ontario College of Pharmacists), we strongly felt that it was necessary and prudent to use a RDP to prevent any possible cutaneous-related adverse reactions or an even more-threatening allergic reaction. The oral pomalidomide suspension that we developed might also be a useful gateway for future patients. Our RDP for pomalidomide has given our patient meaningful control of the myeloma that was life-threatening 16 months before her desensitization.

The patient experienced a dramatic antitumour response within about 3 months and, since desensitization, has continued on low-dose oral pomalidomide 2 mg once daily every 21 days of a 28-day cycle, together with oral dexamethasone 16 mg once weekly on day 22 of the 28-day cycle (Figures 1 and 2). The patient has been maintained on this regimen for more than 16 months since her RDP. No dermatologic complaints or other adverse reactions have been noted at subsequent clinic visits, and her quality of life has been excellent. Aside from intermittent muscle cramps in her lower legs and feet, she has been otherwise physically well and remained active.
SUMMARY

A PDP can be a new treatment strategy for HSR, especially in heavily pretreated patients who showed HSRs to previous lines of IMIs and who might otherwise be unable to continue a life-prolonging drug. The PDP not only offered our patient an additional treatment option, but also greatly improved her quality of life.

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CONFLICT OF INTEREST DISCLOSURES

We have read and understood Current Oncology’s policy on disclosing conflicts of interest, and we declare that we have none.

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