

Josef Singer  <https://orcid.org/0000-0002-8701-2412>
 Erika Jensen-Jarolim  <https://orcid.org/0000-0003-4019-5765>
 Edda Fiebiger  <https://orcid.org/0000-0003-3385-0100>
 Zsolt Szépfalusi  <https://orcid.org/0000-0003-4852-3102>

Correspondence

Zsolt Szépfalusi, Department of Pediatrics and Adolescent Medicine,
 Medical University of Vienna, Vienna, Austria.
 Email: zsolt.szepfalusi@meduniwien.ac.at

Sherezade Moñino-Romero^{1,2} 
 Willem S. Lexmond^{2,3} 
 Josef Singer^{2,4,5,6} 
 Christina Bannert¹
 Abena S. Amoah⁷
 Maria Yazdanbakhsh⁷
 Daniel A. Boakye⁸
 Erika Jensen-Jarolim^{4,5} 
 Edda Fiebiger^{2,3} 
 Zsolt Szépfalusi¹ 

¹Department of Pediatrics and Adolescent Medicine, Medical University
 Vienna, Vienna, Austria

²Department of Pediatrics, Division of Gastroenterology, Hepatology
 and Nutrition, Boston Children's Hospital, Boston, Massachusetts

³Department of Medicine, Harvard Medical School, Boston,
 Massachusetts

⁴Institute of Pathophysiology and Allergy Research, Center of
 Pathophysiology, Infectiology and Immunology, Medical University of
 Vienna, Vienna, Austria

⁵The Interuniversity Messerli Research Institute of the University of
 Veterinary Medicine Vienna, Medical University Vienna and University
 Vienna, Vienna, Austria

⁶Department of Internal Medicine II, University Hospital Krems, Karl
 Landsteiner University of Health Sciences, Krems an der Donau, Austria

⁷Department of Parasitology, Leiden University Medical Center, Leiden,
 The Netherlands

⁸Department of Parasitology, Noguchi Memorial Institute for Medical
 Research, College of Health Sciences, University of Ghana, Legon-Accra,
 Ghana

REFERENCES

1. Platzer B, Ruiter F, van der Mee J, Fiebiger E. Soluble IgE receptors—elements of the IgE network. *Immunol Lett.* 2011;141(1):36-44.
2. Gould HJ, Sutton BJ. IgE in allergy and asthma today. *Nat Rev Immunol.* 2008;8(3):205-217.
3. Hibbert RG, Teriete P, Grundy GJ, et al. The structure of human CD23 and its interactions with IgE and CD21. *J Exp Med.* 2005;202(6):751-760.
4. Frigeri LG, Zuberi RI, Liu FT, Epsilon BP, a beta-galactoside-binding animal lectin, recognizes IgE receptor (Fc epsilon RI) and activates mast cells. *Biochemistry.* 1993;32(30):7644-7649.
5. Moñino-Romero S, Erkert L, Schmidthaler K, et al. The soluble isoform of human Fc epsilon RI is an endogenous inhibitor of IgE-mediated mast cell responses. *Allergy.* 2018;74(2):236-245.
6. Riccio AM, Mauri P, De Ferrari L, et al. Galectin-3: an early predictive biomarker of modulation of airway remodeling in patients with severe asthma treated with omalizumab for 36 months. *Clin Transl Allergy.* 2017;7:6.
7. Dehlink E, Platzer B, Baker AH, et al. A soluble form of the high affinity IgE receptor, Fc-epsilon-RI, circulates in human serum. *PLoS One.* 2011;6(4):e19098.
8. Lexmond W, der Mee J, Ruiter F, et al. Development and validation of a standardized ELISA for the detection of soluble Fc-epsilon-RI in human serum. *J Immunol Methods.* 2011;2:192-199.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

DOI: 10.1111/all.13735

Delayed drug hypersensitivity to bortezomib: Desensitization and tolerance to its analogue carfilzomib

To the Editor,

Bortezomib is a boronic acid dipeptide that selectively inhibits the proteasome and is currently used as standard of care in the treatment of patients with multiple myeloma (MM).^{1,2} It has been shown to inhibit the expression of cell adhesion molecules, co-stimulatory molecules and NF- β activation, to deplete alloreactive T lymphocytes and to decrease Th1 cytokine production.

Cutaneous side effects related to bortezomib administration are frequent, as reported in a phase 3 randomized study,³ in which 57%

and 70% of patients experienced a grade 3 or higher skin toxicity with subcutaneous and intravenous administration, respectively. The severity of skin reactions described in the literature includes a wide range of manifestations, from local delayed flare reaction and perivascular dermatitis, to symmetrical drug-related intertriginous and flexural exanthema (SDRIFE),⁴ Nicolau syndrome,⁵ sweet and sweet-like syndrome,⁶ erythema multiforme-like,⁷ drug reaction with eosinophilia and systemic symptoms (DRESS)⁸ and fatal toxic epidermal necrolysis (TEN).⁹ T cell-mediated immunopathology is central to these severe

delayed reactions, but effector cells and cytokines differ by clinical phenotype.¹⁰ However, these adverse reactions are usually poorly described and the possible mechanism of hypersensitivity not well studied. Only in one of the cases, skin tests were performed to demonstrate a hypersensitivity mechanism.⁴ Nonetheless, the sensitivity and specificity of the skin test with bortezomib are unknown.

We present two patients with MM that experienced a generalized delayed skin reaction after bortezomib subcutaneous (sc) injection, in whom hypersensitivity was shown by means of a positive intradermal test (IDT) to bortezomib.

Patient_1 was an 82-year-old man with a past history of hypertension, dyslipidemia, ischaemic cardiopathy, hypothyroidism, benign prostate hyperplasia and lumbar canal stenosis. He was diagnosed with a high-risk quiescent MM in 2015. In February 2016, bortezomib (Velcade®, Millennium Pharmaceuticals Inc., Cambridge, UK) was started at a dose of 2.5 mg twice per week due to disease progression. The patient presented mild erythrodermic maculopapular lesions at the site of injection after the first and second sc bortezomib administration. Seventeen hours after the administration of the third dose, a generalized pruriginous macular erythrodermia affecting trunk and thighs appeared. Neither fever or other systemic symptoms nor blood test abnormalities were present. He was treated with oral antihistamines with partial clinical improvement. In the following 5 days, two more doses of bortezomib were administered under antihistamine treatment. Twenty-four hours after the last administration, the patient developed fever and the skin rash worsened. A 3-fold increase in the number of eosinophils in peripheral blood was observed. Bortezomib was then discontinued, and the patient was referred to the Allergy Department. The fever subsided 48 hours later, and the skin rash resolved after 2 weeks with subsequent desquamation.

Patient_2 was a 73-year-old woman with a past history of hypertension, dyslipidemia, disease-free breast cancer pT1 N0 and bronchial hyperresponsiveness. She was diagnosed with symptomatic MM in 2017 and started treatment with bortezomib (Velcade®, Millennium Pharmaceuticals Inc.) at a dose of 2.5 mg twice per week in June 2017. Twenty-four hours after the second sc administration of the 4th cycle, she presented a generalized maculopapular pruriginous erythroderma affecting the abdomen, gluteus, internal side of thighs and arms. She was evaluated at the Haematology Department and treated with antihistamines and oral corticosteroids. Bortezomib was discontinued, and the patient was referred to the Allergy department. Skin lesions resolved after 96 hours without desquamation. When questioned, the



FIGURE 1 Intradermal test positivity in patient 2

patient referred an itchy maculopapular rash at the site of injection that lasted 3 days, leaving residual lilaceous hyperpigmentation, since the second administration of the drug.

To prove a delayed hypersensitivity to bortezomib, skin tests with bortezomib at a concentration of 1 mg/mL (undiluted) for the skin prick test (SPT) and 0.1–0.01 mg/mL for the IDT were performed.

In both patients, SPT and IDT resulted negative after 20 minutes but the IDT turned positive in delayed reading, after 12 hours in patient 1 and 8 hours in patient 2 (Figure 1).

Seven patients currently tolerating bortezomib served as negative controls. After signing the informed consent, cutaneous test were performed and SPT and IDT at 0.1 mg/mL resulted negative in both immediate and delayed reading in all patients.

Both cases were discussed with the Haematology Department, and since the benefits outweighed the risks in the case of Patient_1, bortezomib was reintroduced under a desensitization protocol using premedication with corticosteroids and antihistamines (Table 1). The procedure was conducted without major problems and the patient received bortezomib for 48 more weeks, until it was discontinued due to severe gastrointestinal adverse effects.

TABLE 1 Stepped dose schedule with subcutaneous bortezomib used in Patient 1

Day	Dose	Premedication		Symptoms	
		Antihistamines	Oral corticosteroids	Immediate	delayed
1	1 mg	10 mg/day	30 mg/day	No	No
3	1.5 mg	10 mg/day	30 mg/day	No	No
10	2.5 mg	10 mg/day	30 mg/day	No	No
17	2.5 mg	10 mg/day	20 mg/day	No	No
24	2.5 mg	10 mg/day	None	No	No

In Patient_2, bortezomib was discontinued in October 2017 since she had reached partial response with decrease of the monoclonal component. Nine months later, biochemical progression and new bone lesions, with 18% of plasma cells in the bone marrow aspirate, prompted her hematologists to consider starting another proteasome inhibitor. Although no previous reports on tolerance to alternative proteasome inhibitor in patients with a history of severe skin reactions to bortezomib had been published, we set out to try carfilzomib (KYPROLIS®, Amgen Inc., Thousand Oaks, CA, USA), since its molecular structure was different enough to predict a low level of cross-reactivity. SPT (2 mg/mL) and IDT (0.2 mg/mL) to carfilzomib were negative both at immediate and delayed reading. A controlled intravenous challenge with carfilzomib (20 mg/m²) was performed in a hospital setting in July 2018, with good tolerance. The patient received two more cycles without any side effects.

Here, we present two new cases of confirmed delayed hypersensitivity to bortezomib with positive late-reading intradermal tests that suggest an underlying T-cell mechanism. To our knowledge, this is the first report of a desensitization schedule to bortezomib and the first evidence that carfilzomib is well tolerated and can be considered as a safe alternative in patients with delayed hypersensitivity to bortezomib.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

Keywords

bortezomib, carfilzomib, desensitization, drug hypersensitivity, skin test

ORCID

Paula Galvan-Blasco  <https://orcid.org/0000-0003-3006-3160>

Paula Galvan-Blasco^{1,2} 
Mar Guilarte^{1,2,3}
Victoria Cardona^{1,2,3}
Moises Labrador-Horrillo^{1,2,3}
Anna Sala-Cunill^{1,2,3}

Ingrid Johana Gil-Serrano^{1,2}

Olga Luengo^{1,2,3}

¹Allergy Section, Internal Medicine Department, Hospital Universitari Vall d'Hebron, Barcelona, Spain

²Allergy Department, Institut de Recerca Vall d'Hebron, Universitat Autònoma de Barcelona, Barcelona, Spain

³ARADyAL Research Network, Madrid, Spain

Correspondence

Paula Galvan-Blasco, Allergy Section, Internal Medicine Department, Hospital Vall d'Hebron, Barcelona, Spain.

Email: paulagalv27@gmail.com

REFERENCES

- Ri M. Mechanism of action of bortezomib in multiple myeloma therapy. *International Journal of Myeloma*. 2016;6(1):1-6.
- Tung D, Cheung PH, Kaur P, et al. Anti-inflammatory and immunomodulatory effects of bortezomib in various in vivo models. *Pharmacology*. 2011;88(1-2):100-113.
- Moreau P, Pylypenko H, Grosicki S, et al. Subcutaneous versus intravenous administration of bortezomib in patients with relapsed multiple myeloma: a randomised, phase 3, non-inferiority study. *Lancet Oncol*. 2011;12:431-440.
- Malissen N, Bourrain JL, Chiriac A, et al. Symmetrical intertriginous and flexural exanthema due to bortezomib (a Proteasome Inhibitor) Given for Myeloma. *Acta Derm Venereol*. 2016;96(7):995-996.
- Almudimegh A, Le Pelletier F, Dupin N. Nicolau syndrome secondary to subcutaneous bortezomib injection. *J Eur Acad Dermatol Venereol*. 2016;30(2):348-350.
- Knoops L, Jacquemain A, Tennstedt D, Theate I, Ferrant A, Van den Neste E. Bortezomib-induced sweet syndrome. *Br J Haematol*. 2005;131(2):142.
- Gerber PA, Bölke E, Bühren BA, et al. Bortezomib induces erythema multiforme-like cutaneous adverse effects: report of two cases. *Wien Klin Wochenschr*. 2009;121(21-22):723-724.
- Hattori N, Adachi D, Nakashima H, Saito B, Nakamaki T, Tomoyasu S. Drug-induced hypersensitivity syndrome after bortezomib treatment for refractory multiple myeloma. *Leuk Res*. 2009;33(4):574-577.
- Fang B, Song Y, Ma J, Zhao RC. Severe epidermal necrolysis after bortezomib treatment for multiple myeloma. *Acta Haematol*. 2007;118(2):65-67.
- Peter JG, Lehloeny R, Dlamini S, Risma K, White KD, Konvinse KC, Phillips EJ. Severe Delayed Cutaneous and Systemic Reactions to Drugs: A Global Perspective on the Science and Art of Current Practice. *J Allergy Clin Immunol Pract*. 2017;5(3):547-563.

DOI: 10.1111/all.13736

Allergic contact dermatitis to (meth)acrylates involving nail technicians and users: Prognosis and differential diagnosis

To the Editor,

Acrylates and methacrylates are formed by polymerization of acrylic monomers. These monomers can cause allergic contact dermatitis,

and, in the last years, an increasing number of cases have been reported among nail esthetics professionals and users, manifesting as chronic hand eczema¹ with occupational consequences.² The aim of