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Bortezomib-Induced Skin Eruption

S. Sanchez-Politta^a L. Favet^b K. Kerl^a P.-Y. Dietrich^b V. Piguet^aDepartments of ^aDermatology and Venereology and ^bOncology, University Hospital and Medical School of Geneva, Geneva, Switzerland

Key Words

Proteasome inhibitor · Bortezomib · Multiple myeloma · Cutaneous reactions · Adverse drug reactions · Small-vessel lymphocytic vasculitis

Abstract

Bortezomib (Velcade®) is a proteasome inhibitor recently developed and mainly used for the treatment of multiple myeloma. Bortezomib represents a novel class of drugs functioning as proteasome inhibitors. Skin complications of bortezomib treatment are very frequent but poorly characterized. We describe the case of a patient who developed erythematous and edematous plaques after treatment with bortezomib. This case illustrates one of the potential reactions associated with bortezomib administration and underlines the need to recognize and report cutaneous side effects of this new drug.

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Bortezomib (Velcade®) is a proteasome inhibitor recently developed and mainly used for the treatment of multiple myeloma (MM) [1]. Bortezomib is effective through a number of mechanisms leading to apoptosis of plasma cells; its molecular weight is 384.237 g mol⁻¹. It blocks inhibitory κB protein degradation, prevents nuclear factor κB (NF-κB) activation and induces apoptosis in MM cells. Most com-

monly reported side effects are fatigue, thrombocytopenia and peripheral neuropathy. Although frequent, cutaneous reactions associated with this drug are poorly documented in the literature, which consists mainly in phase 1 trials, phase 2 studies and isolated case reports. Here, we describe an MM patient with skin toxicity resulting from bortezomib treatment presenting as an erythematous and edematous plaque eruption and review the existing literature on skin complications associated with bortezomib administration. Adverse cutaneous side effects concern about 10–24% [2–8] of patients and have been described mainly as ‘rash’ [2, 5, 6] or ‘diffuse maculopapular rash’ [3, 4]. To date, only a few individual cases have been reported in detail, 1 case accompanied with a systemic hypersensitivity reaction [3], 12 patients with small-vessel vasculitis [4, 7, 8], 2 patients with Sweet syndrome [9] and in 2 cases vasculitis was histologically demonstrated [10, 11].

Case Report

A 59-year-old man was diagnosed as having IgGκ MM, stage IIIA. From 1997 to 2002, he was successively treated with 3 cycles of vincristine, doxorubicin and dexamethasone chemotherapy followed by high-dose melphalan (200 mg m⁻²) treatment with autologous stem cell support, thalidomide, 7 cycles of cyclophos-

phamide, melphalan and prednisone chemotherapy followed by a second autologous stem cell transplantation. He relapsed in April 2004. Intravenous infusions of bortezomib treatment were started at 1.3 mg m⁻² twice weekly for 2 weeks. IgGκ serum paraprotein decreased from 38 to 21 g l⁻¹ after 6 cycles. Grade I neuropathy appeared, and as a result bortezomib treatment was continued at a lower dose (1 mg m⁻²). On day 11 of the 8th cycle, the patient developed transient nonpruritic erythematous and edematous plaques on the right arm, upper trunk, neck and face measuring 1–3 cm in diameter without any associated symptoms. On day 11 of the 10th cycle, he developed once again a similar rash in the same localization (fig. 1).

He was referred to the dermatology department where a differential diagnosis consisting of urticaria, Schnitzler syndrome, systemic lupus erythematosus, erythema elevatum diutinum or plasma cell infiltration of the skin was discussed. There was an elevated erythroblast sediment rate (81 mm h⁻¹); complete blood count, hepatic and renal function were normal. Antinuclear antibody, antineutrophil cytoplasmic antibody, antinucleosome antibody and complement consumption were absent. Histological examination of a skin biopsy revealed a mononuclear cell infiltrate around vessels (fig. 2) associated with dermal edema and apoptotic basal keratinocytes, consistent with a drug-induced eruption. The skin le-

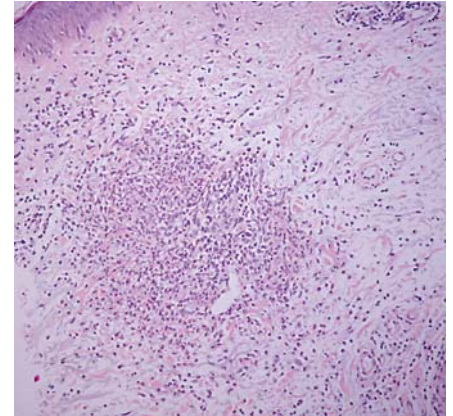
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Fig. 1. Urticarial lesions on the neck of our patient during bortezomib treatment.

Fig. 2. Mononuclear cell infiltrate associated with dermal edema.

2



sions disappeared spontaneously 2 weeks later. Bortezomib treatment was discontinued thereafter as a result of the excellent clinical response of MM. No new lesions were observed during the following months.

Discussion

We describe a case of skin eruption presenting as erythematous and edematous plaques following bortezomib (Velcade) injections.

The recurrence of skin lesions at each cycle, the spontaneous healing after the interruption of injections, the clinical presentation, the absence of general symptoms, the normal blood test results and the histopathological examination point to the causative role of bortezomib. The other considered diagnoses (urticaria, Schnitzler syndrome, systemic lupus erythematosus, erythema elevatum diutinum or plasma cell infiltration of the skin) were ruled out on the basis of patient history, clinical features and histopathological findings.

Despite the high frequency of reported cutaneous side effects (between 7 and 24%) [2–7], the latter are poorly characterized and mostly include ill-defined maculopapular rashes [7–10]. One patient developed a maculopapular rash during the first cycle of treatment, which relapsed during cycle 2, accompanied by dyspnea and arthritis, consistent with a systemic hypersensitivity reaction. His-

tology showed a superficial perivascular lymphocytic and eosinophilic infiltrate with prominent dermal mucin deposition [3]. Four patients treated for B-cell non-Hodgkin's lymphoma developed small-vessel vasculitis [6, 7], which resolved during treatment-free weekly intervals, without any other adverse symptom or antineutrophil cytoplasmic antibody [7]. Six patients treated for MM developed a folliculitis-like rash during the second cycle of bortezomib with perivascular lymphoid infiltrates found in all cases [11]. Treatment was continued and the skin eruption prevented with systemic corticoid therapy. Recently the case of a patient suffering from MM who developed a purpuric rash of the trunk, back, hands and face during cycle 2 has been described [12]. Histology showed leukocytoclastic vasculitis. Lesions healed following prednisone treatment, but reappeared during subsequent cycles of bortezomib treatment.

According to the available data in the literature, cutaneous side effects resulting from bortezomib treatment are not rare, and histopathological evaluation seems to be consistent with vasculitic reactions without systemic involvement, except for 1 case of systemic hypersensitivity reaction [3].

The exact pathogenesis of bortezomib-induced skin eruptions remains unclear, but Min et al. [13] have proposed that bortezomib administration may enhance the release of proinflammatory cytokines. In fact patients with leukoclastic

vasculitis display a marked increase in serum levels of IL-6, TNF- α and C-reactive protein.

In our patient, the late occurrence of the eruption (4 months after the first exposure to the drug) argues against an immunologic mechanism. Blood counts were close to normal during and before the eruption, thereby excluding a lymphocyte recovery eruption or an off-chemotherapy eruption. Bortezomib blocks NF- κ B in the same way that nonsteroidal anti-inflammatory drugs do. Urticarial reactions due to nonsteroidal anti-inflammatory drugs can occur without involvement of an allergically mediated process probably via a direct pharmacological effect. Therefore, it is tempting to propose that the bortezomib-induced skin reaction in this patient is due to a direct pharmacological effect perhaps via the inhibition of the NF- κ B rather than an immunologic mechanism.

In summary, we describe a case of drug-induced erythematous and edematous plaques due to bortezomib treatment. It is important for the clinician to recognize the potential cutaneous side effects associated with this treatment and to be aware that discontinuation of treatment is rarely required as the frequency of serious skin and systemic involvement due to bortezomib treatment is low.

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