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LETTER TO THE EDITOR

Somatic and autonomic small fiber neuropathy induced by bortezomib therapy: an immunofluorescence study

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Abstract Bortezomib is a new chemotherapeutic agent approved for the treatment of relapsed/refractory and newly diagnosed multiple myeloma. One of the major side effects of bortezomib is a peripheral length-dependent sensory axonal neuropathy and, less frequently, a small fiber neuropathy. Autonomic symptoms like postural dizziness, syncope, diarrhoea, ileus, impotence and urinary disturbances have been reported, nevertheless, autonomic neuropathy has never been characterized. We describe by means of immunofluorescence, the involvement of autonomic skin nerve fibers in three patients with small fiber neuropathy induced by bortezomib treatment.

Keywords Small fiber neuropathy · Bortezomib · Velcade · Autonomic neuropathy · Skin biopsy

Dear Editor,

Bortezomib is a new chemotherapeutic agent approved for the treatment of multiple myeloma (MM) [1]. Length-dependent painful neuropathy, mainly related to the loss of c-fibers, but also to deficit in Aδ and Aβ fibers [2, 3], is a common and clinically significant drug-related adverse event and the first cause of dose reduction or treatment suspension [4]. Large and small fibers damage has been related to the duration of bortezomib treatment in rat models, where a short-term treatment induced, predominantly, Schwann cells and myelin damage [5], whereas a long-term exposure produced a prominent axonopathy of the unmyelinated fibers [6]. A small fiber neuropathy (SFN) was previously described in patients treated with bortezomib [4, 7], however, though autonomic symptoms like syncope, impotence, gastrointestinal and urinary disturbances have been reported [4, 8, 9], autonomic neuropathy has never been characterized.

We report three women affected by MM with IgG kappa paraproteins and treated with bortezomib (patients 1 and 2) or an association of bortezomib and thalidomide (patient 3) (Table 1). After 3–5 months of therapy, all patients developed neuropathic pain and discontinued bortezomib therapy (Table 1). Symptoms decreased slightly in patients 1 and 2 after 2 months from suspension, whereas patient 3 experienced a marked improvement. Patients underwent neurological examination and a study of motor (tibial, peroneal, median, ulnar nerves) and sensory (sural, median, ulnar nerves) nerve conductions to evaluate large myelinated nerve fibers. To evaluate somatic and autonomic peripheral small nerve fibers, a 3 mm punch biopsy was taken from the distal leg (10 cm above the lateral malleolus) and thigh (15 cm above the patella). Specimens were fixed, sectioned and incubated with primary antibodies, as previously described [10]. Primary antibodies included the pan-neuronal marker protein gene product 9.5 (PGP 9.5) and specific autonomic antibodies like vasoactive intestinal peptide (VIP) to mark cholinergic fibres innervating sweat glands, and dopamine beta hydroxylase (DBH) to visualize adrenergic fibers innervating blood vessels and arrector pilorum muscles. The ENFs was calculated per linear millimeter of epidermis. As previously described [10], autonomic innervation was graded from 0 (no innervation)

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to 4 (normal pattern, morphology and quantity of fibers) by a semi-quantitative scale showing a low interobserver and intraobserver variability [10]. Fifteen age-matched healthy subjects (62 ± 9 years) served as controls. Somatic and autonomic skin innervation was compared between patients and controls using the Z statistics. A Z score <-1.65 with a $p < 0.05$ was considered significant.

Nerve conduction studies demonstrated a sensory axonal neuropathy in patients 1 and 2, with absent-evoked sensory action potential in sural nerves, whereas they were normal in patient 3 (Table 1).

Skin biopsies showed a significant ENFs reduction in thigh (5 ± 2; n.v. 23.8 ± 4.5) and leg (2.5 ± 1.3; n.v. 15.9 ± 3.9) in all patients, predominantly at the distal leg site (Table 2).

Adrenergic (DBH-ir) fibers were heavily expressed in arrector pilorum muscles, along major axis of blood vessels and around arteriovenous anastomoses (AVAs) in normal controls, while patients showed sparse adrenergic fibers, significantly reduced compared with controls and predominantly in the leg, often displaying morphological abnormalities (i.e., swelling and fragmentation) and deranged pattern of innervation (Table 2). Cholinergic (VIP-ir) fibers were abundant around sweat glands, encircling sweat tubules in normal controls, whereas patients showed poor and deranged cholinergic innervation associated with morphological nerve fibers abnormalities, predominantly in the leg (Table 2).

We studied somatic and autonomic innervation in three patients with relapsed MM treated with bortezomib or bortezomib + thalidomide. As already reported [7], we found a peripheral neuropathy involving large and/or small fibers predominantly in the leg, suggesting a length-dependent neuropathic damage [4, 7]. We also disclosed a severe reduction of autonomic fibres, both adrenergic and cholinergic, innervating epidermal annexes. Skin innervation abnormalities were likely induced by bortezomib therapy, because our patients developed neuropathic pain and autonomic symptoms after 3–5 months from the start of treatment and all patients reported an improvement of those symptoms after bortezomib withdrawal. However, we are not able to exclude that MM was a direct cause of peripheral neuropathy, since we have not done a skin biopsy before the start of bortezomib treatment. Involvement of the autonomic system by bortezomib-induced neuropathy has already been described [4, 8, 9], however, this is the first study reporting an objective analysis of peripheral autonomic fibres in patients treated with bortezomib. We found a reduced autonomic innervation score in both symptomatic and asymptomatic patients (number 2 of Table 1) suggesting that skin autonomic fiber loss may not directly express a specific clinical symptom and may precede clinical autonomic failure. Additional studies including a larger sample of patients, particularly with untreated MM, are needed to confirm the main results of our study.

Table 1 Patients clinical features

Patient no.	Age	Disease duration	Duration of treatment	Somatic symptoms	Autonomic symptoms	Neurological examination	Median sensory NCS	Median motor NCS	Sural NCS	Common peroneal NCS
1	64	7 years	5 months	Paresthesias-disethesies at legs, numbness of hands, ataxia, fatigue	Gastrointestinal disturbances	Hyporeflexia, absence of ankle reflex, hypopallesthesia, gait instability	CV 48.5 **Amp 1.3**	CV 56.1 Amp 13.5	**Absent**	CV 44.4 Amp 3
2	80	4 years	3 months	Painful paresthesias at legs, gait instability	None	Hyporeflexia at legs, hypopallesthesia	CV 47.5 **Amp 2.2**	CV 47.5 Amp 9.2	**Absent**	CV 45.2 Amp 4.9
3	76	1 year	5 months 4 months thalidomide*	Paresthesias-disethesies, allodynia at legs and hands, gait instability	Cutaneous hyperemia	Absence of ankle jerk reflex; diffuse cutaneous hyperaemia	CV 51.3 Amp 9.2	CV 54.7 Amp.17.2	CV 46.4 Amp 8.4	CV 45.5 Amp 6.1

Nerve conduction studies normal values: median nerve (sensory fibers)—CV (m/s) 56.2 ± 5.8, Amp (μV) 38.5 ± 15.6; median nerve (motor fibers)—CV (m/s) 57.7 ± 4.9, Amp (mV) 14 ± 4; sural nerve—CV (m/s) 51.1 ± 5.9, Amp (μV) 17.2 ± 6.7; common peroneal nerve—CV (m/s) 52.0 ± 6.2, Amp (mV) 5.1 ± 2.0

Values in bold outline abnormal values

NCS nerve conduction studies, *CV* conduction velocities (m/s), *Amp* amplitude of sensory (μV) and motor (mV) action potentials

* Concurrent treatment

Table 2 ENF density and semiquantitative score of cholinergic and adrenergic innervations

Patient *n*	Legs			Tight		
	ENF density	VIP-ir fibers	DBH-ir fibers	ENF density	VIP-ir fibers	DBH-ir fibers
1	4**	2.5*	2.5*	7***	3*	3*
2	2***	2.5*	2**	3***	2.5***	2***
3	1.5***	1***	0.5***	5***	2***	1.5***
Controls	15.9 ± 3.9	3.4 ± 0.5	3.4 ± 0.5	23.8 ± 4.5	3.8 ± 0.4	3.8 ± 0.4

* Z score <-1.65, $p < 0.05$

** Z score <-2.33, $p < 0.01$

*** Z score <-3, $p < 0.001$

In conclusion, our immunofluorescence study shows that bortezomib can cause a neuropathy involving somatic as well as autonomic small fibres with a length-dependent pattern.

References

1. Field-Smith A, Morgan GJ, Davies FE (2006) Bortezomib (Velcade™) in the treatment of multiple myeloma. Ther Clin Risk Manag 2(3):271–279
2. Cata JP, Weng HR, Burton AW, Villareal H, Giralt S, Dougherty PM (2007) Quantitative sensory findings in patients with bortezomib-induced pain. J Pain 8(4):296–306
3. Cata JP, Weng HR, Lee BN, Reuben JM, Dougherty PM (2006) Clinical and experimental findings in humans and animals with chemotherapy-induced peripheral neuropathy. Minerva Anestesiol 72(3):151–169 (review)
4. Argyriou AA, Iconomou G, Kalofonos HP (2008) Bortezomib-induced peripheral neuropathy in multiple myeloma: a comprehensive review of the literature. Blood 112(5):1593–1599
5. Cavaletti G, Gilardini A, Canta A, Rigamonti L, Rodriguez-Menendez V, Ceresa C, Marmiroli P, Bossi M, Oggioni N, D'Incalci M, De Coster R (2007) Bortezomib-induced peripheral neurotoxicity: a neurophysiological and pathological study in the rat. Exp Neurol 204(1):317–325
6. Meregalli C, Canta A, Carozzi VA, Chiorazzi A, Oggioni N, Gilardini A, Ceresa C, Avezza F, Crippa L, Marmiroli P, Cavaletti G (2010) Bortezomib-induced painful neuropathy in rats: a behavioral, neurophysiological and pathological study in rats. Eur J Pain 14(4):343–350
7. Richardson PG, Xie W, Mitsiades C, Chanan-Khan AA, Lonial S, Hassoun H, Avigan DE, Oaklander AL, Kuter DJ, Wen PY, Kesari S, Briemberg HR, Schlossman RL, Munshi NC, Heffner LT, Doss D, Esseltine DL, Weller E, Anderson KC, Amato AA (2009) Single-agent bortezomib in previously untreated multiple myeloma: efficacy, characterization of peripheral neuropathy, and molecular correlations with response and neuropathy. J Clin Oncol 27(21):3518–3525
8. Perfetti V, Palladini G, Brunetti L, Sgarella A, Brugnatelli S, Gobbi PG, Corazza GR (2007) Bortezomib-induced paralytic ileus is a potential gastrointestinal side effect of this first-in-class anticancer proteasome inhibitor. Eur J Gastroenterol Hepatol 19(7):599–601
9. Gupta S, Pagliuca A, Devereux S, Mufti GJ, Schey S (2006) Life-threatening motor neurotoxicity in association with bortezomib. Haematologica 91(7):1001
10. Donadio V, Cortelli P, Elam M, Di Stasi V, Montagna P, Holmberg B, Giannoccaro MP, Bugiardini E, Avoni P, Baruzzi A, Liguori R (2010) Autonomic innervation in multiple system atrophy and pure autonomic failure. J Neurol Neurosurg Psychiatry 81(12):1327–1335