

Demyelinating polyradiculoneuritis in patients with multiple myeloma: the other side of bortezomib-induced neurotoxicity

Segolene Gendreau^{a,*}, Giulia Berzero^{b,c,d,*} , Camille Tafani^{e,f}, Igor Raynouard^{b,c}, Damien Ricard^{e,f,g,h,i}, Jean-Valère Malfuson^{g,j}, Karine Viala^k, Rabab Debs^k, Caroline Houillier^{b,c,l}, Luca Diamanti^d, Enrico Marchioni^d, Timothée Lenglet^k, Maya Ouzegdouh^m, Kevin Bihanⁿ, Laurent Gilardin^a and Dimitri Psimaras^{b,c,f}

^aDépartement de Médecine Interne et d'Immunologie Clinique, Groupe Hospitalier Pitié-Salpêtrière, AP-HP, Paris, France; ^bService de Neurologie 2-Mazarin, AP-HP, Groupe Hospitalier Pitié-Salpêtrière, Paris, France; ^cSorbonne Université, Inserm, CNRS, UMR S 1127, Institut du Cerveau et de la Moelle épinière (ICM), Paris, France; ^dNeurooncology Unit, IRCCS Mondino Foundation, Pavia, Italy; ^eService de neurologie, Hôpital d'Instruction des Armées Percy, Service de Santé des Armées, Clamart, France; ^fOncoNeuroTox Group, Center for Patients with Neurological Complications of Oncologic Treatments, Hôpitaux Universitaires Pitié-Salpêtrière-Charles Foix et Hôpital Percy, Paris, France; ^gEcole du Val-de-Grâce, Service de Santé des Armées, F-75005, Paris, France; ^hUniversité Paris-Saclay, ENS Paris-Saclay, CNRS, Centre Borelli, F-94235, Cachan, France; ⁱUniversité de Paris, CNRS, Centre Borelli, F-75005 Paris, France; ^jService d'Hématologie, Service de Santé des Armées, Hôpital d'Instruction des Armées Percy, Clamart, France; ^kDepartment of Clinical Neurophysiology, APHP, Pitié-Salpêtrière Hospital, Paris; ^lService d'Hématologie, Institut Curie, Site Saint Cloud, France; ^mDépartement d'Hématologie, Hôpital Pitié-Salpêtrière, AP-HP, Paris, France; ⁿRegional Pharmacovigilance Center, Department of Pharmacology, Pitié-Salpêtrière Hospital, Paris, France

Introduction

The survival of patients with multiple myeloma has dramatically increased over the last 10 years as a result of novel schemes that include bortezomib, lenalidomide and thalidomide as front-line treatments [1]. Bortezomib, a proteasome inhibitor, is widely used in clinical practice and it is now considered a backbone treatment for both newly diagnosed and relapsing patients [1].

Peripheral neuropathy is a common side effect of bortezomib treatment, estimated to occur in more than 30% of patients [2]. The peripheral neuropathy associated with bortezomib treatment usually consists of a sensory axonopathy characterized by numbness, tingling, and severe neuropathic pain in a stocking and glove distribution, reflecting drug toxicity over small unmyelinated nerve fibers [2]. However, although rarely, immune-mediated neuropathies affecting large proximal myelinated fibers, resulting in prominent motor symptoms, have also been reported during bortezomib treatment [3]. The description of such cases is to date limited to individual case reports or small series, hampering to grasp the relevance of this phenomenon and its clinical and paraclinical characteristics.

In this study, we described 13 patients who developed demyelinating polyradiculoneuritis while receiving bortezomib treatment and performed a review of the literature on this topic. The aim of this report was to raise the attention of hematologists on this rare but severe form of neuropathy that seems to respond favorably to immune therapies.

Methods

We performed a retrospective research in the institutional databases of three Neurology departments (AP-HP GH Pitié-Salpêtrière, Paris, France; Hôpital d'Instruction des

Armées Percy, Clamart, France; Mondino Foundation, Pavia, Italy) for patients with history of multiple myeloma admitted because of symptoms of peripheral neuropathy between the 1st January 2007 and the 31st December 2018. The clinical records of patients identified through this research were reviewed for clinical, electrophysiological, and biological data. After the revision of medical records, only patients who were receiving bortezomib treatment and met Brighton criteria for the diagnosis of Guillain-Barré syndrome (level 1 and 2 of diagnostic certainty) [4] were retained in the study. The assessments performed to exclude alternative diagnoses [4] included immunophenotyping of cerebrospinal fluid (CSF) cells, contrast spinal MRI, testing for HIV, hepatitis C and B, syphilis, systemic autoimmunity, and onconeural, anti-ganglioside, and anti-MAG antibodies. The Overall Neuropathy Limitations Scale (ONLS) was used to assess patient's functional status [5]. The Medical Research Council (MRC) score was used to measure muscle strength [6]. Electrophysiological patterns were defined as demyelinating or axonal using the criteria identified by Hadden and colleagues [7]. Albumino-cytologic dissociation was defined by an elevation of CSF protein levels (>45 mg/dL) in absence of pleocytosis (<5 cells/mm³) [8]. The approval of the Institutional Ethics Committee was obtained for Italian patients. Neither informed consent nor approval of an ethics committee was necessary for French patients according to national law regarding anonymous analysis of patients' medical files (L.1121-1 paragraph 1 and R1121-2, Public Health Code).

Literature review was conducted using the Medline and Embase databases for papers published in English and French up to January 2019. The keyword research was performed using combinations of the following terms: "multiple

CONTACT Dimitri Psimaras  dimitri.psimaras@aphp.fr  Service de Neurologie 2-Mazarin, Hôpitaux Universitaires La Pitié Salpêtrière – Charles Foix, AP-HP, 47-83, Boulevard de l'Hôpital, 75013, Paris, France

*Equal contribution to the manuscript.

 Supplemental data for this article can be accessed [here](#).

© 2020 Acta Oncologica Foundation

Table 1. Clinical and paraclinical features, treatment and outcome in the 13 patients included in the present series.

Pt	Age/ Gender	MM type	Previous CHT	Ongoing treatment scheme (n° of cycles received)	Neurological presentation	CSF analysis			Nerve conduction studies	Immunotherapy	FU duration (months)	Neurological status	
						ONLS at nadir	Proteins (mg/dl)	Cells/mm ³				at last FU (ONLS)	MM status at last FU
1	76/F	IgG λ	No	Bortezomib + melphalan + dexamethasone (1 cycle)	Painful paresthesia and numbness in a stocking and glove distribution; proprioceptive ataxia; dysautonomia (postural hypotension); severe motor deficit in upper and lower limbs (MRC 1–2)	5 + 7	170	<2	Sensory-motor demyelinating neuropathy	IVIg (4 cycles)	3	Improved (3 + 6)	PR
2	61/F	IgG λ	No	Bortezomib + thalidomide + dexamethasone (2 cycles)	Numbness in a stocking and glove distribution; moderate motor deficit in the lower limbs (MRC 4)	3 + 3	120	<2	Sensory-motor axonal neuropathy	IVIg (6 cycles)	9	Improved (2 + 2)	PR
3	71/M	IgG k	No	Bortezomib + thalidomide + dexamethasone (4 cycles)	Paresthesia and numbness in a stocking and glove distribution; severe motor deficit in the lower limbs (MRC 1–2)	3 + 3	47	2	Sensory-motor demyelinating neuropathy	IVIg (1 cycle)	6	Improved (NA)	NA
4	63/M	IgA k	Yes	Bortezomib + thalidomide + dexamethasone (2 cycles)	Paresthesia and numbness in a stocking and glove distribution; severe motor deficit in upper and lower limbs (MRC 1–2)	2 + 2	118	2	Sensory-motor demyelinating neuropathy	IVIg (1 cycle)	11	Improved (0 + 1)	NA
5	62/F	IgG k	No	Bortezomib + thalidomide + dexamethasone (2 cycles)	Painful paresthesia with stocking distribution; dysautonomia (postural hypotension); moderate motor deficit in the lower limbs (MRC 3–4)	3 + 7	192	3	Sensory axonal neuropathy	IVIg (1 cycle)	7	Improved (2 + 2)	NA
6	65/M	IgA λ	No	Bortezomib + lenalidomide + dexamethasone (3 cycles)	Painful paresthesia in a stocking and glove distribution; moderate motor deficit in the lower limbs (MRC 3–4)	3 + 2	100	<2	Sensory-motor demyelinating neuropathy	IVIg (9 cycles)	21	Improved (0 + 2)	NA
7	79/M	IgG λ	Yes	Bortezomib + melphalan + dexamethasone (3 cycles)	Severe proprioceptive ataxia, painful paresthesia in a stocking and glove distribution; dysautonomia (postural hypotension); severe motor deficit in the lower limbs (MRC 1–2)	3 + 3	43	3	Sensory-motor demyelinating neuropathy	IVIg (3 cycles) followed by PE (13 sessions)	16	Improved (0 + 3)	PR
8	64/M	NA	No	Bortezomib + melphalan + thalidomide (3 cycles)	Paresthesia in a stocking and glove distribution; dysautonomia (postural hypotension); moderate motor deficit in the lower limbs (MRC 4)	NA	NA	NA	Sensory-motor demyelinating neuropathy	IVIg (1 cycle)	0.5	Improved (NA)	NA
9	69/F	IgA k	Yes	Bortezomib + lenalidomide + dexamethasone (3 cycles)	Painful paresthesia in a stocking and glove distribution; dysautonomia (postural hypotension); moderate motor deficit in the lower limbs (MRC 4)	4 + 3	120	<2	Sensory-motor axonal neuropathy	IVIg (2 cycles)	3	Improved (NA)	NA

(continued)

Table 1. Continued.

Pt	Age/ Gender	MM type	Previous CHT	Ongoing treatment scheme (n° of cycles received)	CSF analysis			Nerve conduction studies	Immunotherapy	FU duration (months)	Neurological status	
					ONLS at nadir	Proteins (mg/dl)	Cells/mm ³				at last FU (ONLS)	MM status at last FU
10	70/F	IgG k	No	Bortezomib + dexamethasone (2 cycles)	Numbness and tingling with stocking distribution; severe motor deficit in the lower limbs (MRC 2–3)	23	<2	Sensory-motor demyelinating neuropathy	No	0.5	Death due to septic shock	
11	59/M	IgG k	No	Bortezomib + thalidomide + dexamethasone (3 cycles)	Painful paresthesia in a stocking and glove distribution; distal motor deficit in upper (MRC 4) and lower (MRC 2) limbs	38	<2	Sensory-motor axonal neuropathy	High dose steroids (1 cycle)	7	Improved (1 + 2)	PR
12	77/F	IgG k	No	Bortezomib + melphalan + dexamethasone (4 cycles)	Numbness and tingling with stocking distribution; moderate motor deficit in the lower limbs (MRC 3–4)	49	<2	Sensory-motor axonal neuropathy	No	9	Improved (0 + 2)	VGPR
13	72/M	NA	No	Bortezomib + melphalan + dexamethasone (3 cycles)	Numbness and tingling in a stocking and glove distribution; severe motor deficit in the lower limbs (MRC 2–3)	102	<2	Sensory-motor demyelinating neuropathy	IVIg (1 cycle)	1	Improved (0 + 2)	NA

CHT: chemotherapy; CSF: cerebrospinal fluid; F: female; FU: follow-up; M: male; IVIg: intravenous immunoglobulin; MM: multiple myeloma; MRC: Medical Research Council; NA: not available; ONLS: Overall Neuropathy Limitation Scale; PE: plasma exchange; PR: partial response; VGPR: very good partial response.

myeloma", "bortezomib", "Guillain-Barré syndrome", "acute polyradiculoneuritis", "demyelinating neuropathy", and "motor symptoms". Among published cases, we included in this paper only patients who met study criteria (i.e., history of multiple myeloma, ongoing bortezomib treatment and level 1 or 2 of diagnostic certainty for the definition of Guillain-Barré syndrome according to Brighton criteria [4]).

Results

Present series

Table 1 reports previous medical history, clinical/paraclinical features at the time of polyradiculoneuritis, treatment and outcome in the 13 patients identified through our research. The median age at the time of polyradiculoneuritis was 69 years-old (range 59–79). Three patients (3/13, 23%) had previously received bortezomib ($n=2$) or other potentially neurotoxic compound including melphalan ($n=2$), thalidomide or lenalidomide ($n=3$). However, none of them had previously reported symptoms of peripheral neuropathy or had concomitant conditions that might predispose to the development of peripheral neuropathy (e.g., diabetes, alcohol abuse).

Bortezomib had been administered by either subcutaneous (9 cases) or intravenous (1 case) route, as part of association regimens that included dexamethasone (12 cases), thalidomide (6 cases), melphalan (5 cases), and/or lenalidomide (2 cases). Neurological symptoms appeared after a median of 3 cycles of bortezomib (range: 1–4). The median delay between last bortezomib administration and symptom onset was 6 days (range: 1–10).

Neurological presentation was characterized by numbness and painful paraesthesia in a stocking and glove distribution accompanied by progressive bilateral motor deficits which predominated in distal muscles (median MRC: 2.5) and in the lower limbs. Deep tendon reflexes were absent in all affected districts. Symptoms of dysautonomia were present in five patients (5/13, 38%) and primarily consisted of postural hypotension. The median ONLS at symptom nadir was 6 (range: 4–12), reflecting a moderate to severe impairment in daily life activities. Three patients (3/12, 25%) were bedridden, 7 patients (7/12, 58%) needed support for walking, and 2 patients (2/12, 17%) could walk independently although gait looked abnormal.

On nerve conduction studies, eight patients had a demyelinating pattern (8/13, 62%), while the remaining five had prominent axonal findings (5/13, 38%). CSF analysis showed albumino-cytologic dissociation in 9 patients (9/12, 75%).

All patients discontinued bortezomib treatment except for one who had dose reduction (pt n°10). Eleven patients (11/13, 85%) received immunotherapies, which consisted of intravenous immunoglobulin (IVIg) (2 g/kg every 4 weeks) in ten cases and of high-dose corticosteroids in one. The median number of IVIg cycles per patient was 1.5 (range: 1–9). All patients improved under first-line immunotherapy except for one (patient n° 7) who switched from IVIg to plasma exchange because of unsatisfactory clinical response.

Table 2. Clinical and paraclinical features, treatment and outcome in the 9 patients reported in literature.

Authors	Age/ Gender	Previous CHT	Ongoing treatment scheme (n° of cycles received)	Neurological presentation	CSF analysis			Nerve conduction studies	Immunotherapy	FU duration (months)	Neurological status at last FU (residual deficits)	MM status at last FU
					Proteins (mg/dl)	Cells/ mm ³						
Ravaglia et al., (2008)[3]	74/M	No	Bortezomib (3 cycles) + Dexamethasone	numbness and stocking distribution; upper and lower limb proximal and distal motor deficit	80	<2		sensory-motor neuropathy with mixed axonal and demyelinating features; prolonged F waves	Prednisone 1 mg/kg/day	NA	Improved	NA
	67/M	Yes	Bortezomib (4 cycles) + thalidomide + Dexamethasone	painful paresthesias in lower limbs; mild sensory gait ataxia; mild distal weakness	74	<2		sensory-motor neuropathy with mixed axonal and demyelinating features; F waves not evocable	No	10	Minor improvement	Death
	67/M	Yes	Bortezomib (2 cycles) + Dexamethasone	sensory gait ataxia, upper and lower limbs proximal motor deficit, dysautonomia	111	<2		sensory-motor neuropathy with mixed axonal and demyelinating features	IVIg 0.4 g/kg/day for 5 days	2	Improved, walks independently (mild sensory symptoms)	VGPR
	59/F	No	Bortezomib (2 cycles) + Dexamethasone	painful paresthesias in lower limbs, upper limb motor deficit, flaccid paraparesis, urinary retention, ileus	89	<2		sensory-motor axonal neuropathy; F waves not evocable	IVIg 0.4 g/kg/day for 5 days Prednisone 75 mg/day	4	Improved, walks with support (mild sensory symptoms)	Death
Salfee et al., (2010)[9]	60/M	Yes	Bortezomib (3 cycles) + Dexamethasone	pain, numbness and tingling in a stocking and glove distribution, motor deficits in the upper and lower limbs	80	<1		sensory-motor, predominantly axonal, peripheral neuropathy	No	21	Improved, walks independently	PR
Sanada et al., (2010)[10]	59/M	Yes	Bortezomib (3 cycles)	numbness and pain in upper and lower limbs; distal motor deficit; dysautonomia (postural hypotension, urinary retention)	NA	NA		severe sensorimotor polyneuropathy	No	6	Improved, walks with support	VGPR
Mauermann et al., (2012)[12]	54/M	Yes	Bortezomib (1 cycle)	painful paresthesias, numbness and tingling in a stocking and glove distribution; distal motor deficit in upper and lower limbs; dysautonomia	109	3		multiple proximal conduction blocks; preserved conduction velocities and distal latencies; absent F-waves	Oral prednisone 20 mg/day IVIg 0.4 g/kg/day for 5 days IV Methylprednisolone 500 mg twice a week Oral cyclophosphamide 100 mg/day then IV 2,000 mg every 3 weeks (5 cycles)	9	Improved, walks independently (mild sensory disturbances)	PR
Jeter et al., (2012) [13]	65/M	No	Bortezomib (3 cycles) + lenalidomide	severe pain, mild paresthesia, and hypopallesthesia in the lower limbs; moderate to severe motor deficits in upper and lower limbs	133	2		sensory-motor neuropathy with mixed axonal and demyelinating features	Plasma exchange (5 sessions) Prednisone 40 mg/day	9	Improved, walks with support	CR
Thawani et al., (2015) [11]	72/M	Yes	Bortezomib (5 cycles)	numbness and tingling with stocking distribution; proximal and distal motor deficits in lower limbs	NA	NA		sensory-motor predominantly demyelinating polyneuropathy	NA	NA	NA	NA

CHT: chemotherapy; CR: complete response; CSF: cerebrospinal fluid; F: female; FU: follow-up; IV: intravenous; IVIg: intravenous immunoglobulin; M: male; MM: multiple myeloma; NA: not available; PR: partial response; VGPR: very good partial response.

At last follow-up, a median of 7 months (range: 0.5–21) after diagnosis, all surviving patients had improved compared to the peak of disease severity, though most of them were left with mild to moderate neurological sequelae, reflected by a median ONLS score of 3 (range: 1–9). One patient (1/11, 9%) was left bedridden, one patient (1/11, 9%) needed support for walking, while the remaining nine patients (9/11, 82%) were able to walk independently.

Eight patients eventually received other treatments for their multiple myeloma, including second-line agents (5 patients) and autologous stem cell transplantation (6 patients). Information on myeloma status at last follow-up was available for only 5 of the 12 surviving patients: one patient achieved a very-good partial response and the remaining four a partial response.

Literature review

Table 2 reports previous medical history, clinical/paraclinical features at the time of polyradiculoneuritis, treatment and outcome in the 9 patients from literature who met inclusion criteria [3,9–13]. The median age at the time of acute polyradiculoneuritis was 65 years-old (range: 54–74). Six patients (6/9, 67%) had previously received other chemotherapeutic agents including vincristine ($n=3$), adriablastin ($n=3$), melphalan ($n=3$), cyclophosphamide ($n=3$), etoposide ($n=2$), cisplatin ($n=2$), idarubicin ($n=1$), and lenalidomide/thalidomide ($n=3$). Neurological symptoms appeared after a median of 3 cycles of bortezomib (range: 1–5). Clinical presentation was characterized by bilateral distal painful paresthesia associated with progressive moderate to severe distal motor deficits. At the peak of disease severity, four patients (4/6, 67%) were wheelchair bound or bedridden, one needed support for walking (1/6, 17%), and one could walk independently (1/6, 17%). Dysautonomic symptoms were present in 3 patients (3/9, 33%). Nerve conduction studies more commonly showed mixed demyelinating and axonal features. Albumino-cytologic dissociation was present in all seven patients with available CSF data. All patients discontinued bortezomib treatment. Five patients (5/8, 63%) also received immunotherapy regimens based on corticosteroids, IVIg, plasma exchange, cyclophosphamide, or combinations of the latter. Despite being improved compared to the peak of disease severity, all patients were left with mild to moderate residual deficits. These features were similar to the ones observed in our cases (Supplementary Table 1).

Discussion

In this study, we described the clinical and electrophysiological characteristics of 13 patients who developed demyelinating polyradiculoneuritis while receiving bortezomib treatment. Cases were collected among three neurology departments over a period of 12 years, during which more than 2000 patients were treated for multiple myeloma in referring hematology units. A review of the literature identified 9 previously published cases with similar characteristics [3,9–13], confirming the rarity of this entity.

The cases reported in the present study differed from the typical small-fibre sensory neuropathy associated with bortezomib treatment: neurological presentation was dominated by severe bilateral motor deficits that prevented or impaired walking, nerve conduction studies frequently showed demyelinating features, and CSF analysis commonly disclosed albumino-cytologic dissociation. Most patients received IVIg, by analogy with Guillain-Barré syndrome [8], in the attempt to accelerate recovery. However, despite prompt immunotherapy, most of them experienced permanent residual deficits, highlighting the severity of this condition. Clinical and biological indicators able to predict the development of this severe complication are currently lacking but desperately needed for risk stratification and patient monitoring. Low serum BDNF levels have recently been shown to correlate with an increased risk to develop peripheral neuropathy in patients receiving bortezomib or vincristine [14], encouraging further research on soluble biomarkers.

The pathogenic mechanisms underlying bortezomib-induced peripheral neuropathy are poorly understood. Besides sphingolipid dysregulation, mitochondrial dysfunction and disrupted calcium homeostasis [2,15], bortezomib administration has been associated with an increased production of pro-inflammatory cytokines, including TNF- α and IL-1 β [15], which, in the proper context, might favor an immune-mediated demyelination of peripheral nerves.

To what extent the concomitant (or previous) administration of other neurotoxic compounds might facilitate the occurrence of this complication is difficult to assess. Although some studies suggest that associating thalidomide to bortezomib does not increase the risk of peripheral neuropathy compared to bortezomib alone [16], the use of agents with less neurotoxic potential, such as lenalidomide, should probably be preferred while waiting for more solid evidence, as they seem to provide similar oncologic results [17].

Hematologists should be aware that bortezomib treatment can be associated with demyelinating forms of polyradiculoneuritis characterized by severe motor impairment. Prompt neurological evaluation, together with CSF analysis and an attentive research of demyelinating abnormalities on nerve conduction studies, represent the capital elements to ensure an accurate diagnosis and early immunotherapy administration.

Disclosure statement

The authors have no conflict of interest to disclose.

Funding

This work was in part supported by the grant INCa-DGOS-Inserm_12560 of the SIRIC CURAMUS.

ORCID

Giulia Berzero  <http://orcid.org/0000-0001-8798-9058>

References

- [1] Mohan M, Matin A, Davies FE. Update on the optimal use of bortezomib in the treatment of multiple myeloma. *Cancer Manag Res.* 2017;9:51–63.
- [2] Argyriou AA, Iconomou G, Kalofonos HP. Bortezomib-induced peripheral neuropathy in multiple myeloma: a comprehensive review of the literature. *Blood.* 2008;112(5):1593–1599.
- [3] Ravaglia S, Corso A, Piccolo G, et al. Immune-mediated neuropathies in myeloma patients treated with bortezomib. *Clin Neurophysiol.* 2008;119(11):2507–2512.
- [4] Sejvar JJ, Kohl KS, Gidudu J, et al. Guillain-Barré syndrome and Fisher syndrome: case definitions and guidelines for collection, analysis, and presentation of immunization safety data. *Vaccine.* 2011;29(3):599–612.
- [5] Graham RC, Hughes R. A modified peripheral neuropathy scale: the Overall Neuropathy Limitations Scale. *J Neurol Neurosurg Psychiatry.* 2006;77(8):973–976.
- [6] Matthews WB. Aids to the examination of the peripheral nervous system. *J Neurol Sci.* 1977;33(1–2):299.
- [7] Hadden RD, Cornblath DR, Hughes RA, et al. Electrophysiological classification of Guillain-Barré syndrome: clinical associations and outcome. *Ann Neurol.* 1998;44(5):780–788.
- [8] Willison HJ, Jacobs BC, van Doorn PA. Guillain-Barré syndrome. *Lancet.* 2016;388(10045):717–727.
- [9] Saifee TA, Elliott KJ, Rabin N, et al. Bortezomib-induced inflammatory neuropathy. *J Peripher Nerv Syst.* 2010;15(4):366–368.
- [10] Sanada Y, Nakazato T, Suzuki K, et al. [Severe bortezomib-induced peripheral neuropathy in a patient with multiple myeloma]. *Rinsho Ketsueki.* 2010;51(4):264–269.
- [11] Thawani SP, Tanji K, De Sousa EA, et al. Bortezomib-associated demyelinating neuropathy—clinical and pathologic features. *J Clin Neuromuscul Dis.* 2015;16(4):202–209.
- [12] Mauermann ML, Blumenreich MS, Dispenzieri A, et al. A case of peripheral nerve microvasculitis associated with multiple myeloma and bortezomib treatment. *Muscle Nerve.* 2012;46(6):970–977.
- [13] Jeter A, Kang Y. Immune modulation therapy in the management of bortezomib-induced peripheral neuropathy. *Exp Hematol Oncol.* 2012;1(1):20.
- [14] Azoulay D, Giryas S, Nasser R, et al. Prediction of chemotherapy-induced peripheral neuropathy in patients with lymphoma and myeloma: the roles of brain-derived neurotrophic factor protein levels and a gene polymorphism. *J Clin Neurol.* 2019;15(4):511–516.
- [15] Zajączkowska R, Kocot-Kępska M, Leppert W, et al. Mechanisms of chemotherapy-induced peripheral neuropathy. *Int J Mol Sci.* 2019;20(6):E1451.
- [16] Wang A, Duan Q, Liu X, et al. (Bortezomib plus lenalidomide/thalidomide)- vs. (bortezomib or lenalidomide/thalidomide)-containing regimens as induction therapy in newly diagnosed multiple myeloma: a meta-analysis of randomized controlled trials. *Ann Hematol.* 2012;91(11):1779–1784.
- [17] Aguiar PM, de Mendonça Lima T, Colleoni GWB, et al. Efficacy and safety of bortezomib, thalidomide, and lenalidomide in multiple myeloma: an overview of systematic reviews with meta-analyses. *Crit Rev Oncol Hematol.* 2017;113:195–212.