

Bortezomib-induced peripheral neuropathy in multiple myeloma: a comprehensive review of the literature

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Bortezomib has demonstrated significant activity in clinical trials, mainly against recurrent or newly diagnosed multiple myeloma (MM). Peripheral neuropathy is a significant toxicity of bortezomib, requiring dose modification and potential changes in the treatment plan when it occurs. The mechanism underlying bortezomib-induced peripheral neuropathy (BIPN) is unknown. Metabolic changes resulting from the accumulation of bortezomib in the dorsal root ganglia cells, mitochondrial-mediated dysregulation of Ca⁺⁺ homeostasis, and dysregulation of

neurotrophins may contribute to the pathogenesis of BIPN. It is increasingly recognized that BIPN may be a proteasome inhibitor class effect, producing primarily a small fiber and painful, axonal, sensory distal neuropathy. Incidence of BIPN is mainly related to various risk factors, including cumulative dose and evidence of preexisting neuropathy. Assessment of BIPN is based primarily on neurologic clinical examination and neurophysiologic methods. To date, apart from the use of dose reduction and schedule change algorithm, there is no effective

tive treatment with neuroprotective agents for BIPN. Analgesics, tricyclic antidepressants, anticonvulsants, and vitamin supplements have been used as symptomatic treatment against bortezomib-associated neuropathic pain with some success. This review looks critically at the pathogenesis, incidence, risk factors, diagnosis, characteristics, and management of BIPN, and highlights areas for future research. (Blood. 2008;112:1593-1599)

Introduction

The ubiquitin-proteasome system is the major intracellular protein degradation pathway in eukaryotic cells, playing an important role in transcriptional regulation of the key transcription factor, nuclear factor- κ B (NF- κ B). The 26S proteasome, an adenosine triphosphate-dependent protease, is fundamental for the ubiquitin-proteasome pathway.¹ Proteasome inhibition induces apoptosis, cell adhesion, transcription, and angiogenesis of cancer cells, exerting at the same time a nontoxic effect on most normal cells.²

Bortezomib, a boronic acid dipeptide, is a 20S proteasome complex inhibitor that acts by disrupting various cell signaling pathways, thereby leading to cell cycle arrest, apoptosis, and inhibition of angiogenesis. The hallmark of bortezomib action is the inhibition of NF- κ B, thereby interfering with NF- κ B-mediated cell survival, tumor growth, and angiogenesis.³

Bortezomib monotherapy was approved by the US Food and Drug Administration in 2003 for the treatment of refractory multiple myeloma (MM) after 2 prior treatment schedules. A year later, the European Medicines Agency granted approval for the use of bortezomib against MM, subject to annual reassessment of the pros and cons. In addition to MM, the use of bortezomib has a solid rationale against nonhematologic malignancies.⁴

Peripheral neuropathy (PN) is a significant dose-limiting toxicity of bortezomib that typically occurs within the first courses of bortezomib, reaches a plateau at cycle 5, and thereafter does not appear to increase.⁵ We herein review and discuss the pathogenesis, incidence, risk factors, diagnosis, characteristics, and management of bortezomib-induced peripheral neuropathy (BIPN). We also highlight areas of future research to pursue.

Search strategy and selection criteria

References for this review were identified by searches of PubMed from 2000 until March 2008 with the terms "proteasome inhibitors," "proteasome inhibitors and peripheral neuropathy," "Velcade," "bortezomib-induced neurotoxicity," "bortezomib-induced peripheral neuropathy," and "chemotherapy-induced peripheral neuropathy."

Pathogenesis of peripheral neuropathy

Current knowledge of the mechanism underlying BIPN is very limited.⁵ Mitochondrial and endoplasmic reticulum damage seems to play a key role in BIPN genesis, since bortezomib is able to activate the mitochondrial-based apoptotic pathway.⁶ It has recently been reported that cotreatment with a panel of Ca⁺⁺-modulating agents identified the mitochondrial uniporter as a critical determinant in bortezomib cytotoxicity in myeloma cell lines. This fact supports the view that mitochondrial-mediated dysregulation of Ca⁺⁺ homeostasis is a critical regulator of bortezomib cytotoxicity.⁷

Dysregulation of neurotrophins has also been proposed as another important mechanism of BIPN genesis, since the main action of bortezomib is the inhibition of NF- κ B activation, thereby blocking the transcription of nerve growth factor-mediated neuron survival.⁸ It is increasingly recognized that BIPN may be a proteasome inhibitor class effect and that autoimmune factors and inflammation may also trigger BIPN.^{2,3,9,10}

Table 1. Components of the Total Neuropathy Score (TNS)

Component	TNS parameters				
	0	1	2	3	4
Sensory symptoms	None	Limited to fingers or toes	Extend to ankle or wrist	Extend to knee or elbow	Above knees/elbows
Motor symptoms	None	Slight difficulty	Moderate difficulty	Require help/assistance	Disabled
Autonomic symptoms, n	0	1	2	3	4 or 5
Pin sensation	Normal	Reduced in fingers or toes	Reduced up to wrist/ankle	Reduced up to elbow/knee	Reduced above elbow/knee
Vibration sensibility	Normal	Reduced in fingers or toes	Reduced up to wrist/ankle	Reduced up to elbow/knee	Reduced above elbow/knee
Strength	Normal	Mild weakness	Moderate weakness	Severe weakness	Paralysis
Tendon reflexes	Normal	Ankle reflex (AR) reduced	AR absent	AR absent, other reflexes reduced	All reflexes absent
QST vibration sensation	Normal to 125% ULN	126%-150% ULN	151%-200% ULN	201%-300% ULN	>300% ULN
Sural a-SAP	Normal or reduced <5%	76%-95% of LLN value	51%-75% of LLN value	26%-50% of LLN value	0%-25% of LLN value
Peroneal a-CMAP	Normal or reduced <5%	76%-95% of LLN value	51%-75% of LLN value	26%-50% of LLN value	0%-25% of LLN value

a-SAP indicates amplitude of sensory action potentials; a-CMAP, compound muscle action potential; LLN, lower limit of normal; and ULN, upper limit of normal.

To our knowledge, only one full paper published to date describes neurophysiologic and pathologic findings after bortezomib administration in animal models.¹¹ In this study, spinal cord was morphologically normal. The sciatic nerve examination and morphometric determinations demonstrated mild to moderate pathologic changes involving predominantly the Schwann cells and myelin, although axonal degeneration was also noted. Bortezomib-induced changes were also observed in dorsal root ganglia (DRG) neurons, being represented by satellite cell intracytoplasmic vacuolization due to mitochondrial and endoplasmic reticulum damage. Considering the trophic supportive role that satellite cells may have in toxic DRG damage, these changes support that secondary neural dysfunction may occur.¹²

Another preliminary *in vivo* (mice) and *in vitro* (PC-12 cells/rat pheochromocytoma cell line) study, presented as a meeting abstract, demonstrated that the primary target for proteasome inhibitor-associated peripheral neuropathy was the DRG neuronal cell bodies.¹³ *In vivo*, proteasome inhibition resulted in chromatolysis of DRG neurons, followed by cytoplasmic accumulation of eosinophilic material. Evidence of neurofilaments and juxtannuclear electron-dense cytoplasmic deposits were also noted within the DRG neurons. Both *in vivo* and *in vitro* lesions after proteasome inhibition appeared to be related to blood and cellular proteasome inhibition levels of 70% to 80%.¹³

Finally, results from a neurophysiologic study applying quantitative sensory testing in patients receiving bortezomib for treatment of either MM or non-Hodgkin lymphoma demonstrated that bortezomib-induced pain is associated with deficits of all 3 major fiber types, ie, A β , A δ , and C caliber primary afferent fibers.¹⁴ In any case, both the pathogenesis of BIPN and the anatomical structures that are primarily or secondarily affected by bortezomib are vaguely defined, and further studies are warranted before definite conclusions can be drawn.

Diagnosis

Assessment of BIPN is based primarily on different approaches of clinical examination, summarized by several comprehensive neurotoxicity grading scales. The most widely used grading systems for assessing neurotoxicity are the National Cancer Institute–Common Toxicity Criteria [NCI-CTC],¹⁵ Eastern Cooperative Oncology Group criteria,¹⁶ Ajani,¹⁷ and the World Health Organization criteria.¹⁸

Most of the published studies assessing BIPN^{19,20} have used either the NCI-CTC version 2 or 3 criteria or the 11-item

neurotoxicity subscale (FACT/GOG-Ntx) developed in the late 1990s by the Gynecologic Oncology Group (GOG) so as to measure neurotoxicity secondary to the administration of regimens consisting of doxorubicin/cisplatin/paclitaxel.²¹ The Ntx subscale covers from the clinical point of view sensory, motor, and hearing neuropathy and dysfunction associated with neurotoxicity,²² whereas the NCI-CTC version 2 or 3 criteria crudely evaluate the extent of sensory and motor peripheral nerve damage secondary to chemotherapy administration.

Despite the different scales, accurate grading of BIPN is still a matter of debate, mainly because the degree of BIPN is subjective and dependent on patients' reporting, thereby resulting in variances in interpreting clinical aspects and poor reliability. Limitations also result from intra- and interobserver variation of scales.²³

Recently, the Total Neuropathy Score (TNS), a composite measure that includes symptoms, signs, ability aspects, and electrophysiologic measures, has been shown to have good validity with the second version of the NCI-CTC, the Eastern Cooperative Oncology Group, and the Ajani score in patients having chemotherapy-induced peripheral neuropathy (CIPN).²⁴ Furthermore, compared with NCI-CTC, TNS showed a higher sensitivity to CIPN changes in a more recent study of the same group, thereby proposing TNS as a reliable method for assessing both the severity and course of CIPN.²⁵ Table 1 describes the components of the TNS scoring system. Laboratory analyses such as cerebrospinal fluid (CSF) examinations do not provide any additional information and are not helpful in anticipating the severity of neurotoxicity. Therefore, their use is not recommended.

Our group favors a grading scale using both clinical and electrophysiologic evaluation, such as the TNS. We strongly support the view that clinical examination and electrophysiologic measures are capable of objectively assessing both the severity and course of peripheral nerve damage secondary to the toxic effect of chemotherapeutic agents.²⁶ However, we acknowledge that electrophysiologic examination is not always available in the general hematology/oncology setting, and therefore may be difficult to apply in practice. Considering that TNS does not include an evaluation of pain intensity, the assessment and grading of BIPN using the TNS and the pain Visual Analog Scale (VAS) or the 11-point pain intensity numerical scale (PI-NRS) may represent, in our opinion, the optimal method.

To our knowledge, TNS score has been used in a single study that assessed BIPN in 27 patients treated with bortezomib and thalidomide for newly diagnosed MM.²⁷ Thus, it is acknowledged that TNS is not an established measure in BIPN and that its validity and reliability should be tested further in future

studies assessing neurotoxicity in patients treated with bortezomib. Preliminary studies using a detailed clinical and electrophysiologic examination combined with scales for grading pain intensity have been conducted and presented at various meetings.²⁸ In any case, because the need for a simple, widely usable, and effective grading system is clear, further systematic clinimetric studies are warranted to accurately detect and grade the incidence, severity, and course of BIPN.

Incidence, severity, and risk factors

Current knowledge shows that peripheral nerve damage is one of the most significant nonhematologic toxicities of bortezomib, which often leads to dose modification and impact on clinical endpoints and quality of life (QOL) of patients. Grades 1 and 2 BIPN can occur in up to 75% and 33% of patients with recurrent or newly diagnosed disease under bortezomib therapy, respectively, whereas grades 3 and 4 neurotoxicity may affect up to 30% of patients with recurrent disease and up to 18% of patients with newly diagnosed disease.^{20,29,30} Fatal grade 4 sensorimotor and autonomic neurotoxicity has also been reported in a single case report.³¹

The results of the SUMMIT³² and CREST³³ phase 2 trials accurately provide data about the incidence, severity, and risk factors of BIPN. SUMMIT, a multicenter, open-label nonrandomized trial, enrolled 202 patients with relapsed and refractory MM treated with 1.0 or 1.3 mg/m² of IV bortezomib twice weekly for 2 weeks, in cycles repeated every 3 weeks for a maximum of 8 cycles.³² The CREST trial³³ applied a similar study design and treatment schedule in 54 patients. Pooled safety data from these trials showed that BIPN was one of the most common and important drug-related adverse events. Peripheral neuropathy was diagnosed in 90 of 256 (35%) enrolled patients. Grade 1 or 2 neuropathy occurred in 22% of patients, whereas grades 3 and 4 BIPN occurred in 13% and 0.4%, respectively. Dose reduction due to neurotoxicity was required in 12% of patients, and 5% of patients discontinued treatment.¹⁹

Other similar studies published subsequently confirmed the results of the latter analysis. In a multicenter study enrolling 27 patients with relapsed or refractory Waldenstrom macroglobulinemia, bortezomib has been administered at a dose of 1.3 mg/m² for 8 cycles. Sensory BIPN represented the most common grade 3/4 toxicity, followed by leukopenia, neutropenia, dizziness, and thrombocytopenia. Therapy discontinuation resulted in improvement or complete resolution of BIPN.³⁴ In a study of similar design and sample size, Chen et al³⁵ reported that 20 of 27 patients (74%) manifested new or worsening BIPN. Five of them developed grade 3 neurotoxicity leading to dose modification. No grade 4 BIPN was noted.

In another interesting report, Badros et al²⁰ retrospectively reviewed the incidence, severity, and risk factors of BIPN in 78 patients with recurrent and/or refractory MM who were treated with bortezomib alone or in combination with thalidomide and/or chemotherapy. PN affected 52% of patients, including grade 3 and 4 neurotoxicity in 15% and 7%, respectively. Nine patients stopped bortezomib, and dose reduction was applied in 11 patients because of BIPN. Grade 4 neurotoxicity was observed in 6 patients that was either sensory (n = 4) or sensorimotor (n = 2). The retrospective design and the elevated number of patients with preexisting neuropathy or diabetes mellitus (DM) were the main limitations of this study and may have biased the interpretation of results.

The incidence of chemotherapy-induced neurotoxicity is usually related to risk factors including treatment schedule, time of infusion, and preexisting peripheral neuropathy from hereditary or nutrition-associated medical conditions of paraneoplastic nature, DM, alcohol abuse.³⁶ In line with this, several studies have consistently associated the cumulative dose amount of the first 5 therapy courses and preexisting neuropathy with increased incidence of BIPN.

In the study by Richardson et al,¹⁹ treatment-emergent peripheral neuropathy was reported in 21% of patients receiving bortezomib at a single dose of 1.0 mg/m² and 37% in patients receiving bortezomib at 1.3 mg/m². Maximum BIPN usually occurred at a cumulative dose of 30 mg/m² (approximately at course 5), and thereafter remained consistent until course 8. Cumulative bortezomib dose was significantly correlated with the FACT/GOG-Ntx score ($r = 0.108$; $P < .004$). From a clinical point of view it should be emphasized that BIPN typically occurs within the first 5 cycles of bortezomib administration and is rare thereafter, suggesting a dose threshold rather than a classic cumulative dose effect of bortezomib.

Baseline neuropathy and comorbidities such as DM that evoke peripheral nerve damage may also predict the occurrence of BIPN and are usually correlated with its severity.^{19,20} In addition, a preliminary report of bortezomib safety in patients with relapsed/refractory MM indicated that less heavily pretreated patients in an earlier stage of disease manifest milder BIPN.³⁷ Prolonged administration of bortezomib is not significantly associated with increased incidence and severity of BIPN.²²

One could suggest that treatment schedules consisting of thalidomide plus bortezomib would lead to increased incidence and severity of neurotoxicity, because of the well-known neurotoxic effect both drugs exert. However, in opposition to this hypothesis, a correlation analysis of several studies according to prior or concomitant thalidomide administration did not reveal any significant relationship to the incidence or severity of treatment-emergent peripheral neuropathy.^{19,20} On the contrary, thalidomide may play a protective role against BIPN, in that responding patients who were treated with bortezomib plus thalidomide had decreased rates of early withdrawals because of toxicities and the required minimal dose reductions.²⁰ The reason for this result is unclear, but one possible suggestion is that the anti-inflammatory action of thalidomide may protect against BIPN.

We would concur with the view that the severity of BIPN with this combination is less than what would be expected, yet the overall cumulative peripheral neuropathy incidence rate is considerable, with reports of approximately 60% over time.²⁰ In our opinion, the use of bortezomib and thalidomide as a combination is of great clinical interest, but clearly using 2 neurotoxic agents simultaneously has limitations.

In contrast, the use of bortezomib and lenalidomide, an analog of thalidomide, has been associated with lower accumulated rates of BIPN.²⁰ Preliminary results may show there was no evidence of grade 3 or 4 BIPN after a treatment regimen consisting of this combination approach, which may be attributable primarily to the abbreviated doses of bortezomib that were used in this study and/or the anti-inflammatory action of lenalidomide.³⁸ In any case, further larger studies are needed to support the finding of symptomatic improvement of BIPN after lenalidomide administration.

Furthermore, intriguing studies involving tanespimycin, a heat shock protein (HSP)-90 inhibitor, have emerged as exciting opportunities for the reduction of BIPN, possibly through the up-regulation of HSP70, thereby constituting an exciting new perspective in the field.^{38,39}

Table 2. Clinical and electrophysiologic features of BIPN

Clinical symptoms	Electrophysiologic findings
Often, mild to moderate distal sensory loss, suppression of deep tendon reflexes, proprioception abnormalities	NCS: Reduction of a-SAPs and CMAPs. Mild distal slowing of sensory and motor conduction velocities and increase in distal motor latencies.
Mild to very severe pain, mainly at fingertips and toes	EMG: Active denervation changes with fibrillation potentials and increased size and complexity of motor unit potentials from distal muscles of the lower limbs.
Usually, mild motor weakness in distal muscles of the lower limbs; rarely, severe distal and proximal weakness	QST: Increased touch thresholds, increased slotted pegboard time, cold pain thresholds at abnormally warm levels and reduction in sharpness detection
Very rarely, autonomic failure	

BIPN indicates bortezomib-induced peripheral neuropathy; NCS, nerve conduction study; a-SAPs, amplitude of sensory action potentials; CMAPs, compound muscle action potentials; EMG, electromyography; and QST, quantitative sensory testing.

According to published data, the incidence of grade 3 or 4 neurotoxicity was 14% for patients aged less than 75 years and 25% in older patients, thereby supporting the view that elderly patients may be more prone than younger patients to manifesting increased incidence and severity of BIPN.⁴⁰ Our experience indicates that the incidence and severity of chemotherapy-induced neurotoxicity in patients having solid cancer is not differentiated according to age.⁴¹ Other studies assessing BIPN in hematologic malignancies have reached to the same conclusion.^{20,42} Hence, considering the relative small sample size of Mateos et al, study⁴⁰ and published data,²⁰ we suggest that the inclusion of advanced age as a triggering factor of BIPN merits further exploration.

It has been also reported that BIPN may be associated with impaired renal function and worst creatinine clearance in patients with MM.⁴³ Drug metabolism and abnormal liver function may also trigger BIPN and therefore their role as risk factors for BIPN induction should be explored in future studies.

Over the past years, bortezomib has demonstrated a significant anticancer activity against several solid tumors, including metastatic prostatic, breast, renal, and ovarian cancers.⁴ Current knowledge, shows that the use of bortezomib in solid malignancies is associated with lower rates of BIPN as opposed when administered for MM.⁴⁴

Considering that in a preliminary report, a significant portion (15%) of chemotherapy-naïve patients with newly diagnosed MM were found to have neuropathy at baseline, the disease itself may represent another contributing factor to BIPN genesis.²⁷ Furthermore, even higher rates of peripheral neuropathy were reported by other investigators. Peripheral neuropathy at baseline was seen in more than 20% of patients with newly diagnosed MM scheduled to be treated with single-agent bortezomib therapy.⁴⁵ This fact could potentially explain the favorable toxicity profile of bortezomib in solid tumors compared with what is seen with MM.

Clinical and electrophysiologic characteristics

Symptoms and signs of BIPN are clinically characterized of evidence of neuropathic pain, distal sensory loss to all modalities in the lower more than in the upper limbs, suppression of deep tendon reflexes (DTR) in proportion to sensory loss and changes in proprioception. These clinical findings are in keeping with a painful neuropathy due to dysfunction of sensory nerves.⁵ Pain, positive sensory symptoms in a stocking-and-glove distribution, and proprioception changes usually do not subside between courses of therapy and may severely affect normal daily living activities.⁴⁶ Grades 1 through 3 motor neuropathy, consisting of mild to severe distal weakness in the lower limbs, may occur in up of 10% of patients.^{35,47} There are rare reports of cases experiencing life-threatening grade 4 motor and autonomic neurotoxicity.³¹

The cardinal symptom of BIPN is neuropathic pain, located mainly in the fingertips and toes. The intensity of pain ranges from very mild to very severe. In a recent study, bortezomib-induced pain was rated in the majority of patients as moderate to severe, according to VAS. Pain had a mean rating of 7.8 (on a score scale of 0 for no pain and 10 for worst imaginable pain) with 11 of 16 patients rating their maximum daily pain at a score of 8 or more. Elevated sharpness detection threshold and lower skin temperature are specific characteristics of pain regions as compared with nonpainful areas of skin.¹⁴

From the electrophysiologic point of view, nerve conduction study predominantly reveals low amplitude of sensory action potentials, in keeping with a distal, sensory, axonal neuropathy. The sural nerve is predominantly affected.¹⁹ Prolonged latency or loss of the H-reflex (the electrophysiologic correlate of the ankle-jerk reflex) represents another sensitive electrophysiologic marker of sensory fiber involvement. Reduced amplitude of compound muscle action potentials, indicating axonal motor involvement, has also been reported.^{35,48}

Mild distal slowing of sensory and motor conduction velocities and increase in distal motor latencies may also occur, in keeping with a primary or secondary demyelination process due to primary myelin-Schwann cell damage or degeneration of fast-conducting fibers. Demyelination neuropathy has been reported as being pronounced in the distribution of ulnar nerves.²⁰ Active denervation changes in distal muscles of the lower limbs with fibrillation potentials and increased size and complexity of motor unit potentials may also be evident in electromyographic testing with concentric needle electrodes.⁵

Finally, the neurophysiologic approach with quantitative sensory testing in patients receiving bortezomib reveals increased touch thresholds, increased slotted pegboard time, abnormal cold pain thresholds, and reduction in sharpness detection, implying that BIPN is associated with dysfunction in all 3 major fiber types (A β , A δ , and C) in sensory nerves.¹⁴ Table 2 describes the overall clinical and electrophysiologic characteristics of BIPN.

Outcome and natural course of BIPN after discontinuation of treatment

The manifestation of severe neurotoxicity often leads to dose modification or even to therapy discontinuation. The most reliable report on the outcome of BIPN comes from a recent study that assessed 256 patients enrolled in the SUMMIT and CREST studies.¹⁹ In this analysis, 90 patients experienced treatment-emergent peripheral neuropathy. Thirty-five of them experienced either grade 3 or 4 neuropathy and/or neuropathy leading to discontinuation of treatment. BIPN-induced discontinuation of treatment was noted in 5% of patients (14/256). BIPN-associated dose reduction was required in 12% of patients

(31/256), representing 34% of patients (31/90) who developed new or worsening neuropathy. In 7% of patients (19/256), at least one course of bortezomib was withheld because of peripheral neuropathy, representing 21% of patients (19/90) with new or worsening neuropathy.¹⁹

In another multicenter retrospective monitoring of adverse events in patients treated with bortezomib for MM, it was reported that 8 of 95 patients (7.5%) stopped therapy because of neurotoxicity. Neuropathy greater than grade 2 was more frequent in patients who received 4 or more prior therapy regimens than in those who received 3 or fewer courses of treatment.⁴⁹ Similar rates of therapy discontinuation because of BIPN were reported in another phase 2 study testing the efficacy of bortezomib plus dexamethasone as first-line therapy in patients with MM. Grade 2 or 3 BIPN was observed in 7 cases (14%). However, in 3 patients experiencing grade 3 neurotoxicity, neuropathic symptoms improved significantly after drug withdrawal or dose reduction.⁵⁰

Data from large, well-conducted controlled studies performed thus far support the view that symptoms of BIPN improve or completely resolve in most patients after a median interval of 3 months after discontinuation of bortezomib treatment.^{19,20,32} However, there are reports in which the recovery from pain and other sensory neuropathic symptoms required up to 2 years after bortezomib discontinuation.³⁵ In a recently published study, detailed clinical assessment and neurophysiologic examination was performed in 35 patients with advanced MM experiencing grade 3 BIPN after completion of bortezomib therapy. The results of this study showed that neuropathic pain and other sensory symptoms of BIPN completely resolved or improved in 31% of patients (11/35) with clinically significant neuropathy. Ten patients did not experience improvement in painful peripheral neuropathy after the final dose of bortezomib and were lost at follow-up. Overall, the median duration from therapy discontinuation to resolution or improvement of BIPN was 47 days (range, 1-529 days).¹⁹

To our knowledge, there is a paucity of data concerning the reversibility of subclinical electrophysiologic abnormalities after the discontinuation of bortezomib administration. However, the evidence of clinical improvement is considerable, in contrast with other forms of neurotoxicity in MM patients, especially after thalidomide treatment.^{51,52} At present, relevant literature contains no report of delayed appearance of BIPN in asymptomatic patients after completion of therapy.

Options for neuroprotection

To date, there is no effective prophylactic treatment against BIPN and treatment is merely symptomatic. The armamentarium of pharmacologic agents commonly used for symptomatic treatment of painful sensory BIPN includes various opioids, tricyclic antidepressants, anticonvulsants, serotonin-norepinephrine reuptake inhibitors, nonsteroidal anti-inflammatory agents, vitamins, and nutritional supplements.⁵³ Table 3 outlines the pharmaceutical interventions for the symptomatic treatment of bortezomib-induced neuropathic pain.

Several studies attempted to test the efficacy of all the above-mentioned treatment strategies, alone or in combination, in relieving the painful symptoms of BIPN. Disappointingly, only modest pain relief was observed after the administration of such overloaded analgesic treatment schedules.^{14,20} In contrast, the clinical

Table 3. Medications for symptomatic relief of painful BIPN

Medication class	Medications
Opioids	Oxycodone, hydrocodone, morphine, fentanyl
Tricyclic antidepressants	Amytriptyline, nortriptyline, desipramine
Anticonvulsants	Gabapentin, oxcarbazepine, pregabalin
SNRIs	Duloxetine
NSAIDs	Celecoxib, rofecoxib, ibuprofen, acetaminophen
Vitamins	Vitamin B6, vitamin C
Nutritional supplements	α-Lipoic acid, glutamine, L-carnitine

BIPN indicates bortezomib-induced peripheral neuropathy; SNRIs, serotonin-norepinephrine reuptake inhibitors; and NSAIDs, nonsteroidal anti-inflammatory drugs.

experience from other study groups is different; in them, analgesic regimens were important and helped with symptomatic BIPN.¹⁹ Considering the discrepancy between results, further studies of this important topic are clearly warranted before definitive conclusions can be drawn.

Existing recommendations concerning the use of nutritional supplements favor their administration at low doses, since there is robust evidence that the administration of pyridostigmine (vitamin B6) and vitamin C at high doses may be harmful and therefore should definitely be omitted. Vitamin B6 can cause additional sensory neuropathy in patients with impaired renal function and in association with a protein-deficient diet.^{54,55} Vitamin C may interfere with bortezomib metabolism and may also abrogate bortezomib-mediated inhibition of proteasome activity; therefore, its concomitant use with bortezomib should be avoided.⁵⁶

Interestingly, intravenous immunoglobulin (IVIG) administration has been proposed by a preliminary report as an effective therapy for the symptomatic management of BIPN. In this study, 9 patients received IVIG for management of treatment-emergent BIPN and improvement of at least 1 grade was observed in all of them. Surprisingly, salvage therapy with IVIG (2 g/kg divided over 4 days) improved grade 4 neurotoxicity to grade 2 neurotoxicity in 1 patient, who also became pain-free within 2 days after completion of IVIG courses.⁹ However, it should be mentioned that the results of this study have been reported only as a meeting abstract and no peer-reviewed publication about this case has subsequently appeared. Therefore, considerable caution is recommended with this reference⁹ both in terms of the incidence reported and the use of IVIG.

Among nonpharmacologic approaches, dose and treatment schedule modifications are the mainstays of treating BIPN. Use of the dose reduction algorithm has resulted in a significant reduction of BIPN severity and duration.⁵⁷ Therefore, adherence to dose modification guidelines (Table 4) developed in the CREST and SUMMIT studies and validated in the prospective Assessment of Proteasome Inhibition for Extending Remissions (APEX) trial^{57,58} are clearly warranted to prevent treatment-emergent BIPN and allow treatment to continue.⁵⁹ In any case, because no pharmacologic medications exist for convincingly relieving neuropathic symptoms of BIPN, further prospective studies on the topic are clearly warranted. Further studies are also needed to help identify an effective and safe neuroprotective agent that would not interfere with the impressive cytotoxic activity of bortezomib.

Conclusions and future research perspectives

Peripheral neuropathy is a common and important nonhematologic, dose-limiting adverse effect of bortezomib-based chemotherapy,

Table 4. Dose modification guidelines for BIPN

Severity of BIPN	Action
Grade 1 (paresthesias or areflexia without pain or loss of function)	Continue as scheduled
Grade 1 with pain or grade 2 (interferes with function but not with DLA)	Reduce dose per course to 1.0 mg/m ²
Grade 2 with pain or grade 3 (interferes with DLA)	Withhold bortezomib treatment until BIPN resolves, then reinstate at a dose of 0.7 mg/m ² once weekly
Grade 4 (sensorimotor neuropathy that significantly interferes with DLA)	Discontinue therapy

BIPN indicates bortezomib-induced peripheral neuropathy; and DLA, daily living activities.

obviously lessening the QOL of patients with hematologic and solid malignancies. However, despite the increasing number of patients exposed to bortezomib therapy, there is a relative paucity of data concerning BIPN. Because combination approaches in the treatment of MM have been associated with lower rates of BIPN, further studies testing such approaches will also be helpful.

Studies using a detailed clinical and electrophysiologic examination combined with a grading scale of pain intensity are needed to determine the exact characteristics of BIPN. The pathogenesis of BIPN is still unknown and, therefore, further *in vitro* studies and animal models would provide an improved understanding of the pathophysiologic mechanism of BIPN. To date, apart from the use of dose reduction and schedule change algorithms, there is no effective treatment with neuroprotective agents against BIPN. Hence, the elucidation of BIPN pathogenesis would also facilitate the identification of effective and safe neuroprotective agents against BIPN.

Second-generation proteasome inhibitors such as carfilzomib and salinosporamide A (NPI-0052) have demonstrated tolerability and antitumor activity *in vivo* in studies using human MM xenografts⁶⁰ and represent another important area for future research. These novel agents exhibit a highly selective mechanism of action for the proteasome, and it is believed that this selectivity may reduce toxicities seen with bortezomib, including neurotoxic-

ity.⁶¹ Carfilzomib is currently being tested in a phase 2 clinical trial, building on the positive safety data and encouraging evidence of activity observed to date in a phase 1b trial; peripheral neuropathy has been reported but has not been severe.

Overall, BIPN remains a very challenging area in the field. Compared with other neurotoxic drugs in oncology (ie, taxanes, platinum, and thalidomide), work with BIPN has in fact been intensive, for which some credit to both the investigators and the manufacturer (Millennium Pharmaceuticals, Cambridge, MA), as bortezomib toxicity has been taken very seriously from the earliest phases of bortezomib development.

Authorship

Contributions: All authors collected data, wrote the manuscript, and approved the final version. H.P.K. provided overall supervision.

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