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REVIEW

Management of treatment-emergent peripheral neuropathy in multiple myeloma

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Peripheral neuropathy (PN) is one of the most important complications of multiple myeloma (MM) treatment. PN can be caused by MM itself, either by the effects of the monoclonal protein or in the form of radiculopathy from direct compression, and particularly by certain therapies, including bortezomib, thalidomide, vinca alkaloids and cisplatin. Clinical evaluation has shown that up to 20% of MM patients have PN at diagnosis and as many as 75% may experience treatment-emergent PN during therapy. The incidence, symptoms, reversibility, predisposing factors and etiology of treatment-emergent PN vary among MM therapies, with PN incidence also affected by the dose, schedule and combinations of potentially neurotoxic agents. Effective management of treatment-emergent PN is critical to minimize the incidence and severity of this complication, while maintaining therapeutic efficacy. Herein, the state of knowledge regarding treatment-emergent PN in MM patients and current management practices are outlined, and recommendations regarding optimal strategies for PN management during MM treatment are provided. These strategies include early and regular monitoring with neurological evaluation, with dose modification and treatment discontinuation as indicated. Areas requiring further research include the development of MM-specific, patient-focused assessment tools, pharmacogenomic analysis of patient DNA, and trials to assess the efficacy of pharmacological interventions.
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Introduction

Peripheral neuropathy (PN) is an important complication of multiple myeloma (MM) and associated conditions[1–3] that can be caused both by the disease and by the therapies used to treat MM. [1,2,4] Over the past decade, new treatment options, specifically the proteasome inhibitor bortezomib, and the immunomodulatory drugs thalidomide and lenalidomide, have revolutionized MM therapy, improving response and long-term outcomes. This review focuses on treatment-emergent PN with these novel MM agents and other agents in their classes (including carfilzomib, marizomib and pomalidomide), plus other US Food and Drug Administration/European Medicines Agency-approved agents and other recommended MM therapies associated with PN (Supplementary Table 1). A large body of data exists characterizing bortezomib-induced PN (BiPN), whereas PN associated with other agents, such as thalidomide-induced PN (TiPN), is less well understood. Because of the difficulty and complexity of diagnosing and differentiating autonomic PN in this setting, this discussion is focused on sensory, motor and sensorimotor neuropathy. Autonomic dysfunction may occur with both bortezomib and thalidomide treatment and can be managed with supportive measures.

Etiology of PN in MM patients

MM-associated PN

Rates of PN caused by MM have been reported from 1–2%(ref. 1) to 20%.[5] Although the exact etiology of MM-associated PN is unknown, amyloid deposition, immunoglobulin M antibodies directed at myelin-associated glycoprotein, a glycoconjugate component of nerves involved in interactions between Schwann cells and axons, and cytokine-mediated injury have been suggested as possible mechanisms, in addition to neurological

complications in the form of radiculopathy from direct compression.[1,2,4] The etiological mechanisms involved are likely to be complex in terms of causative pathways, as small fiber injury, segmental demyelination and axonal degeneration can occur.[1,2,4]

PN is also associated with the related disorders of monoclonal gammopathy of undetermined significance,[1] primary and familiar amyloidosis and POEMS (polyneuropathy, organomegaly, endocrinopathy, M protein and skin changes) syndrome.[1,6] The pathology of PN in MM patients is distinct from that seen with other paraproteinemias,[2] highlighting the importance of MM-specific management strategies.

Proteasome-inhibitor-induced PN

Proteasome inhibitors inhibit the 26S proteasome, either reversibly (bortezomib, MLN9708,[7] CEP-18770[(ref. 8)]) or irreversibly (carflizomib, marizomib), disrupting protein regulation and preventing proteasomal degradation of ubiquitinated proteins. In mice, ubiquitinated aggregates accumulated in the cytoplasm of the dorsal root ganglia (DRG), suggesting that this is the primary target in proteasome-inhibitor-induced PN.[9–11] The BiPN seen in a SwissOF1 mouse model showed pathological characteristics similar to those seen in the clinic.[12,13] Accumulation of neuronal cytoplasmic aggregates has been demonstrated with proteasome inhibitors of different chemical scaffolds, suggesting that this is both a mechanism-based and class effect.[9,10]

However, in a rat model of PN, carfilzomib did not damage the DRG.[14] One hypothesis is that the boron-based moiety of bortezomib, but not the epoxyketone-based component of carfilzomib, inhibits non-proteasomal targets, which may be involved in BiPN.[14,15] In preclinical studies using an *in vitro* neuron model, the mitochondrial serine protease HtrA2/Omi was directly or indirectly impacted by bortezomib, but not carfilzomib.[15] Additionally, Cathepsin G activity was reduced and neurite growth was impeded significantly in the presence of bortezomib, but not carfilzomib.[15] Another hypothesis is that, unlike the reversible inhibitor bortezomib, a substantial proportion of carfilzomib molecules may irreversibly bind to proteasomes in red blood cells and hepatocytes, thereby restricting their tissue distribution so that fewer molecules reach the DRG.[16]

Proteasome-inhibitor-induced PN may also affect microtubule-associated proteins and cause microtubule stabilization, with similar preclinical results seen with proteasome inhibitors of different chemical structure.[17]

Immunomodulatory-drug-induced PN

Thalidomide has multiple mechanisms of action in MM, including inhibition of angiogenesis, induction of apoptosis, increasing natural killer cell and T-cell numbers, antiproliferative effects and inhibition of cytokine secretion. Some preclinical and clinical data suggest that thalidomide may affect the DRG, leading to DRG degeneration.[18] Other studies have suggested that TiPN is due to downregulation of tumor necrosis factor-α (TNF-α), leading to Wallerian degeneration and loss of myelinated fibers.[19] The systemic inflammatory disorder leukocytostatic vasculitis has been reported, albeit rarely, in patients treated with thalidomide,[20] which may have a role in neuropathy. There are no available data regarding the etiology of PN associated with lenalidomide and pomalidomide, likely, at least in part, because lenalidomide is associated with substantially lower rates of PN and much less severe PN compared with thalidomide.

PN induced by other MM agents

Limited information is available about the mechanisms by which other neurotoxic agents cause PN in MM. Preclinical data suggest that vincristine causes distal axonal degeneration through localized axonal toxicity[21] that is likely caused by vincristine binding to tubulin and disrupting microtubule polymerization.[6] Preclinical data suggest that cisplatin-induced PN results from direct toxic damage to the DRG,[6] but may also involve degeneration of both the peripheral and central processes of large-diameter sensory neurons.[22]

Symptoms, incidence and clinical characteristics

Symptoms

MM-associated PN is predominantly sensory or sensorimotor, and typically involves segmental demyelination and distal axonal degeneration without involvement of the dorsal roots.[2] Symptoms are usually symmetric and include paresthesias, numbness, burning sensation and weakness; these are generally mild, but in rare cases can be disabling or even life-threatening.

Treatment-emergent PN symptoms are usually symmetric, distal and progressive, although there are some differences among therapies.[2,4] BiPN is predominantly sensory and mild (although severe sensory and motor PN have been reported in up to 15% of patients).[23] Symptoms include a burning sensation, hyperesthesia, hypoesthesia, paresthesia, discomfort and neuropathic pain or weakness,[23] which may start distally and progress proximally.

Thalidomide is known to cause nerve damage that may be permanent, and the symptoms of TiPN can occur after treatment has stopped.[24] Thalidomide is reported to cause a primarily sensory/sensorimotor, length-dependent axonal neuropathy, typically with tingling or painful distal paresthesia affecting the feet and sometimes the hands, as well as sensory loss in the lower limbs.[19,25,26] Motor changes may affect patients with TiPN[25] and can present as muscle weakness or, more frequently, tremor.

Neurotoxicity with vincristine develops as a distal symmetric sensorimotor neuropathy.[27] Frequently, sensory impairment and paresthesia occur; with prolonged exposure this can be followed by neuritic pain and motor difficulties.[28] Although there are no specific data on MM patients, cisplatin can lead to long-term peripheral sensory nerve damage in patients with successfully treated epithelial ovarian cancer.[29]

Incidence

In a multicenter phase 2 study of single-agent bortezomib designed to carefully assess the impact of BiPN in frontline MM patients, 64% showed treatment-emergent sensory BiPN, including 3% grade 3 (no grade 4).[5] In phase 3 trials of bortezomib-based combinations in frontline MM, BiPN has been reported in up to 70% of patients, including grade $\geqslant 3$ sensory BiPN in up to 16% (Table 1).[30–40] The incidence of BiPN in the relapsed setting is similar to that seen in the frontline setting (Table 2).[41–44] Importantly, development of BiPN does not appear to adversely impact response rates or outcomes.[32,43]

The incidence of treatment-emergent PN with newer proteasome inhibitors has been relatively low. In phase 1/2 studies of carfilzomib[45–50] in hematological malignancies, PN rates of $\leqslant 10\%$ overall and 0–3% grade 3 were reported; similarly, significant treatment-emergent PN has not been reported in three phase 1 trials of marizomib to date.[51–53] Results from larger studies will be important to confirm these preliminary

Table 1 Clinical incidence of PN in key phase 3 studies in newly diagnosed patients with MM

Study/Regimen	*Planned dose and schedule*[a]	*Planned/Median duration of therapy*	N	*Incidence of treatment-emergent PN (%)*			*Discon. due to PN*
				All grades	*Grade 1/2*	*Grade 3/4*	
Dexamethasone-based combinations							
Phase 3, VD ± DCEP vs VAD ± DCEP[33]	VD; 3-week cycles; then DCEP (cisplatin 10 mg/m^2 days 1–4); 4-week cycles	4/4 cycles induction+2/2 cycles consolidation	240	46	21/16[b]	7[b]	NR
	VAD; vincristine: 0.4 mg/m^2 days 1–4; 4-week cycles; then DCEP (cisplatin 10 mg/m^2 days 1–4); 4-week cycles		242	28	18/8	2	NR
Phase 3, TD vs dex[60]	TD; T: 50→100→200 mg/day; 4-week cycles	NR/6.9 months	235	54	32/19	5 (3 PN NOS)	3%
	Dex; 4-week cycles	NR/6.4 months	235	34	30/4	0	NR
Phase 3, TD vs MP[119]	TD; T: 200 mg/day; 4-week cycles	9 cycles/NR	145	72	65	7	NR
	MP; 4-week cycles		143	35	32	1	NR
Phase 3, RD vs Rd[70]	RD; R: 25 mg/day, days 1–21; 4-week cycles	4 months	223	NR	NR	2	NR
	Rd; R: 25 mg/day, days 1–21; 4-week cycles	6 months	222	NR	NR	2	NR
Doxorubicin+dexamethasone-based combinations							
Phase 3, PAD vs VAD[37]	PAD; V: 1.3 mg/m^2, days 1, 4, 8, 11, 4-week cycles	3/3 cycles	371	76[c]	50[c]	26[c]	NR
	VAD; V: NR; 4-week cycles		373	66[c]	54[c]	12[c]	NR
Phase 3, TAD vs VAD[56]	TAD; T: 200–400 mg/day; 4-week cycles	3/3 cycles	201	NR	NR	7 (neurology)	NR
	VAD; vincristine 0.4 mg/day, days 1–4; 4-week cycles		201	NR	NR	12 (neurology)	NR
Melphalan–prednisone-based combinations							
Phase 3 VISTA, VMP vs MP[32]	VMP; V: 1.3 mg/m^2, days 1,4,8,11,22,25,29,32 cycles 1–4, days 1,8,22,29 cycles 5–9; 6-week cycles	9/9 cycles	344	47 (44% sensory, 6% motor, 3% PN)	14/19	13 (<1 grade 4) (13% sensory PN, 2% motor PN)	11% V (11% sensory, 1% motor, <1% PN); 3% VMP
	MP; 6-week cycles	9/8 cycles	338	5	5	0	NR
Phase 3, MPT vs MP[57,58]	MPT; T: 100 mg/day; 4-week cycles then T maintenance	6/6 cycles (3.6 additional months T)	129	NR	NR/⩾7	10	2% of patients with grade 2 PN
	MP; 4-week cycles	6/6 cycles	126	NR	NR	0	NR
Phase 3, MPT vs MP[61]	MPT; T: 100 mg/day; 6-week cycles	12 cycles/T: 9 cycles (13.5 months)	113	39	19/18	2/0	11%
	MP, 6-week cycles	12 cycles/18 months placebo	116	21	16/3	2/0	3%
Phase 3, MPT vs MP[55]	MPT; T: ⩽400 mg/day; 6-week cycles	12 cycles/T: 8 cycles (11 months)	125	55	50	6/0	T: 18%
	MP; 6-week cycles	NR	196	NR	NR	0	NR
Phase 3, MPR vs MPR+R maintenance vs MP[120]	MPR; R: 10 mg/day; 4-week cycles	36 weeks/NR	153	NR	NR	0	NR
	MPR-R; R: 10 mg/day 4-week cycles; 10 mg/day maintenance	36 weeks+maintenance/NR	152	NR	NR	0	NR
	MP; 4-week cycles	36 weeks/NR	154	NR	NR	0	NR
Bortezomib+thalidomide combinations							
Phase 3, VTD vs TD[31]	VTD; V; T: 100→200 mg/day; 3-week cycles	3/3 cycles	241	34	NR/6	10[d]	1
	TD; T: 100→200 mg/day; 3-week cycles		239	14	NR/4	2[d]	NR
Phase 3 VD vs vTD[40]	VD; V: 1.3 mg/m^2/day, day 1,4,8,11; 3-week cycles	4 cycles/4 cycles	99	70	NR/23	11	4
	vTD; v: 1 mg/m^2 days 1,4,8,11; T: 100 mg/day; 3-week cycles		100	53	NR/11	3	0
Phase 3, VMP vs VTP, followed by VP or VT maintenance[34]	VMP; V: 1.3 mg/m^2, days 1,4,8,11,22,25,29,32, one 6-week cycle, then d 1,8,15,22, five 5-week cycles	6 cycles/NR	130	NR	NR/8	6/1	NR
	VTP; V: 1.3 mg/m^2 as VMP arm; T: 50→100 mg/day	6 cycles/NR	130	NR	NR/14	4/5	NR
	VP; V: 1.3,mg/m^2, days 1, 4, 8, 11, every 3 months	Up to 3 years/NR	87	NR	NR	2	NR
	VT; V: 1.3,mg/m^2, days 1, 4, 8, 11, every 3 months; T: 50 mg/day	Up to 3 years/NR	91	NR	NR	7	NR
Phase 3, VMPT+VT maintenance vs VMP[35]	VMPT; V: 1.3 mg/m^2 days 1, 8, 15, 22; T: 50 mg/day; 5-week cycles[e]; VT maintenance; V: 1.3 mg/m^2 day 1, 15; T: 50 mg/day	9+maintenance until relapse/9 cycles	254[e]	NR	NR	8[e]	8
	VMP; V as VMPT arm[e]	9/9 cycles	257[e]	NR	NR	5	7

Table 1 (*Continued*)

Study/Regimen	Planned dose and schedule[a]	Planned/Median duration of therapy	N	Incidence of treatment-emergent PN (%)			Discon. due to PN
				All grades	*Grade 1/2*	*Grade 3/4*	
Phase 3 VMPT or VMP weekly vs bi-weekly[30]	VMPT or VMP weekly; V: 1.3 mg/m^2 days 1, 8, 15, 22; T: 50 mg/day; 5-week cycles	9/9 cycles	372	NR	NR/13	8 (3 sensory, 3 neuralgia, 3 both)	5
	VMPT or VMP bi-weekly; V: 1.3 mg/m^2 days 1, 4, 8, 11, 22, 25, 29, 32, cycles 1–4, 1, 8, 22, 29, cycles 5–9; T: 50 mg/day; 6-week cycles	9/9 cycles	139	NR	NR/26	28 (16 sensory, 5 neuralgia, 8 both)	15

Abbreviations: DCEP, dexamethasone, cyclophosphamide, etoposide, cisplatin; Dex, dexamethasone; Doxil, liposomal doxorubicin; MM, multiple myeloma; MP, melphalan, prednisone; MPT, melphalan, prednisone, thalidomide; NR, not reported; PAD, bortezomib, doxorubicin, dexamethasone; PN, peripheral neuropathy; RD, lenalidomide, dexamethasone; Rd, lenalidomide, low-dose dexamethasone;
T, thalidomide; TAD, thalidomide, doxorubicin, dexamethasone; TD, thalidomide, dexamethasone; V, bortezomib; VAD, vincristine, doxorubicin, dexamethasone; VD, bortezomib, dexamethasone; VISTA, VELCADE as Initial Standard Therapy In Multiple Myeloma: Assessment with melphalan and prednisone; VMP, bortezomib, melphalan, prednisone; VMPT, bortezomib, melphalan, prednisone, thalidomide; VnBMCP/VnBAD, vincristine, carmustine, melphalan, cyclophosphamide, prednisone alternating with vincristine, carmustine, doxorubicin, dexamethasone; VTD, bortezomib, thalidomide, dexamethasone.

[a]Bortezomib is dosed at 1.3 mg/m^2 on days 1, 4, 8 and 11 unless otherwise indicated; details are only provided for neurotoxic agents or agents specifically addressed in the review.

[b]Grade 2 PN 20.5% and Grade 3 or 4 PN 9.2% after VD+DCEP+first transplantation.

[c]Rates shown for entire treatment protocol. Rates during bortezomib maintenance (following PAD) were 14% grade 2, 9% grade 3 or 4; rates during thalidomide maintenance (following VAD) were 26% grade 2, 15% grade 3 or 4.

[d]1% and 0% grade 3/4 PN with VTD and TD, respectively, in the consolidation phase (two 5-week cycles; V: 1.3 mg/m^2 days 1, 8, 15, 22; T: 10 mg/day).

[e]66 VMP patients and 73 VMPT patients received bi-weekly bortezomib using the regimen employed in VISTA; 4% Grade 3 neuropathy during VT maintenance.

results. Many patients in these trials had received prior bortezomib; some had experienced BiPN but did not develop PN in the carfilzomib or marizomib trials. The lack of dose-limiting PN and the lower rate of neurotoxicity reported in these preliminary studies is promising; however, further studies, additional data, and longer follow-up are required to confirm the incidence of PN with these newer agents.

The incidence of TiPN is generally similar to that reported for BiPN, with incidences of up to 75% reported in patients who received >12 months of treatment.[54] In frontline MM patients, rates of overall and grade ⩾3 PN of up to 55% and 10%, respectively, have been seen (Table 2).[31,34–36,55–61] Systematic reviews of studies of single-agent thalidomide and of thalidomide–dexamethasone in relapsed MM reported an overall incidence of 22% grade 1/2 and 6% grade 3/4 TiPN,[62] and an overall incidence of 27%,[63] respectively. In contrast, no severe PN and markedly reduced overall incidences compared with thalidomide have been reported in studies of lenalidomide (Tables 2 and 3; rates of grade ⩾3 PN: 0–2%).[64–71] Preliminary data also suggest low-to-intermediate incidences with pomalidomide.[72,73]

When administered as part of the vincristine, doxorubicin, dexamethasone or pegylated/liposomal doxorubicin, vincristine, dexamethasone regimens, vincristine has been associated with rates of grade ⩾2 neurotoxicity of 10–13% and 15%, respectively.[33,74,75] The relatively low reported incidence and severity may be because of the generally short duration of treatment or the infusional administration route, which results in low peak concentrations. In a phase 3 Eastern Cooperative Oncology Group study, with a planned treatment duration of 10 cycles (~1 year), the vincristine, carmustine, melphalan, cyclophosphamide and prednisone regimen was associated with 24% grade ⩾2 PN,[76] possibly due to the bolus administration of vincristine.

Although administration of neurotoxic agents in combination might be expected to increase the risk of PN, clinical evidence suggests this is not always the case. Studies of bortezomib plus thalidomide (VT) alone or with dexamethasone, prednisone, or melphalan–prednisone have not reported a notable increase in the rate or severity of PN (Table 1).[31,34,35,77–80] Furthermore, lower-than-expected rates of severe PN have been reported for bortezomib plus lenalidomide combinations,[81,82] with grade 3 PN rates of 3% and 2% with bortezomib, lenalidomide and dexamethasone (RVD) in frontline and relapsed/refractory patients, respectively.[81,82] An exception is the phase 1/2 EVOLUTION study, in which 17% of patients experienced grade 3/4 PN;[83] unlike the other RVD studies, dexamethasone dosing was not partnered with bortezomib dosing. The low rates seen in most RVD studies may be associated with the anti-inflammatory effects of lenalidomide or the dosing schedule of dexamethasone, or both.

Low rates of BiPN have also been reported when bortezomib is administered in combination with pegylated liposomal doxorubicin (4% versus 9% for bortezomib alone)[39] or, in mostly small studies, with novel, investigational agents such as heat-shock protein 90, p38 MAPK and histone–deacetylase inhibitors.[84–89] For some studies this may be partially associated with a limited treatment duration, or possibly with a patient selection bias. Negligible PN has been seen when these agents have been combined with lenalidomide.

Effects of dose and schedule

The incidence of BiPN increased with cumulative dose using the standard dose and schedule, generally occurring after five

Table 2 Clinical incidence of PN in key phase 3 studies in patients with relapsed MM

Study/regimen	*Planned dose and schedule*[a]	*Median duration of therapy received*	N	*Prior neurotoxic agents*	*Incidence of treatment-emergent PN (%)*			*Discontinued. due to PN*
					All grades	*Grade 1/2*	*Grade 3/4*	
Single-agent bortezomib								
Phase 3 APEX, V vs dex[43b]	V; 3-week cycles; then days 1, 8, 15, 22, 5-week cycles	24+15/18 weeks	333	Vinca alkaloid 75%; T 48%	37	10/18	8/<1	9%
	Dex; 5-week cycles, then 4-week cycles	20+20/15 weeks	336	Vinca alkaloid 72%; T 50%	9	NR	<1/<1	NR
Phase 3 V+liposomal doxorubicin (V+Doxil) vs V alone[39]	V+Doxil; V: 1.3 mg/m^2 days 1, 4, 8, 11, 3-week cycles	8/5 cycles (24/15 weeks)	324	T/R 40%	35	NR	4	NR
	V: as for V+Doxil	8/5 cycles (24/15 weeks)	322	T/R 43%	39	NR	9	NR
Phase 3 MMY-3021 subcutaneous vs intravenous V ± dex[44]	Subcutaneous V; 3-week cycles; ± dex	8 cycles/24 weeks	148	T/R 42%	38	32	6	NR
	Intravenous V, 3-week cycles; ± dex	8 cycles/24 weeks	74	T/R 53%	53	37	16	NR
Dexamethasone-based combinations								
Phase 3 MM010, R+dex vs dex[64]	R: 25 mg d 1–21; dex; 4-week cycles	Until disease progression/ ⩽11.3 months[c]	176	T 30%, V 5%	NR	NR	0	NR
	Dex; 4-week cycles	Until disease progression/ ⩽4.7 months[c]	175	T 38%, V 4%	NR	NR	0	NR
Phase 3 MM009, R+dex vs dex[68]	R: 25 mg days 1–21; dex; 4-week cycles	Until disease progression/ ⩽11.1 months[c]	177	T 42%, V 11%	NR	NR	2/0	NR
	Dex; 4-week cycles	Until disease progression/ ⩽4.7 months[c]	176	T 46%, V 11%	NR	NR/NR	1/0	NR

Abbreviations: APEX, Assessment of Proteasome Inhibition for Extending Remissions; Dex, dexamethasone; Dox, liposomal doxorubicin; NR, not reported; PN, peripheral neuropathy; R, lenalidomide; T, thalidomide; V, bortezomib.
[a]Bortezomib is dosed at 1.3 mg/m^2 on days 1, 4, 8, and 11 unless otherwise indicated; details are only provided for neurotoxic agents or agents specifically addressed in the review.
[b]Bortezomib data from updated APEX analysis.[43]
[c]Based on median time to progression.

Table 3 NCI CTCAE assessment of peripheral neuropathy; these definitions are not specific to MM and the classification of a PN event as grade 1–4 may be subject to investigator bias

	Grade					
	0	*1*	*2*	*3*	*4*	*5*
Version 3.0						
Neuropathy—sensory	Normal	Asymptomatic; loss of deep tendon reflexes or paresthesia (including tingling) but not interfering with function	Sensory alteration or paresthesia (including tingling), interfering with function, but not interfering with ADL	Sensory alteration or paresthesia interfering with ADL	Disabling	
Neuropathic pain	None	Mild pain not interfering with function	Moderate pain; pain or analgesics interfering with function, but not interfering with ADL	Severe pain; pain or analgesics severely interfering with ADL	Disabling	
Version 4.0						
Peripheral sensory neuropathy		Asymptomatic; loss of deep tendon reflexes or paresthesia	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated	Death
Peripheral motor neuropathy		Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self-care ADL; assistive device indicated	Life-threatening consequences; urgent intervention indicated	Death
Neuralgia		Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self-care ADL	—	—

Abbreviations: ADL, activities of daily living; MM, multiple myeloma; PN, peripheral neuropathy.
In NCI CTCAE version 4.0, 'instrumental' ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money and so on, whereas 'self-care' ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications and not being bedridden.

3-week cycles (cumulative bortezomib dose ~26 mg/m^2) and reaching a plateau after approximately eight cycles (cumulative dose ~42 mg/m^2) in the APEX trial in relapsed MM,[43] and reaching a plateau after approximately four 6-week cycles (cumulative dose ~45 mg/m^2) in the VISTA trial in frontline MM.[32] The subsequent risk of late-developing BiPN is low.[32,42,43] Similarly, there is a relatively limited risk of developing BiPN among patients who have received prior bortezomib; prospective and retrospective studies have shown that retreatment with bortezomib is associated with rates of neuropathy of 16–39%, including 5–9% grade 3 neuropathy (which included multiple MedDRA terms not typically included in BiPN),[90,91] and extended bortezomib therapy does not increase the rate or severity of PN,[92] suggesting that prolonged exposure or retreatment does not result in cumulative neurotoxicity; however, this may be because of a patient selection bias.[30,34,35,92,93]

Studies that used lower doses or a weekly dosing schedule, in which patients received a lower dose intensity of bortezomib, have reported a lower incidence of BiPN (Table 1).[30,34,35,40,42,94]

A subanalysis of the Gruppo Italiano Malattie EMatologiche dell'Adulto study of bortezomib, melphalan, prednisone, thalidomide versus bortezomib, melphalan, prednisone in elderly, previously untreated patients showed a significantly lower incidence of PN with weekly versus bi-weekly bortezomib (cumulative 18-month incidence of sensory PN: 27%, including 4% grade $\geqslant$3, versus 46%, including 21% grade $\geqslant$3).[30] Compared with VISTA,[32] the incidence of grade 3/4 BiPN with bortezomib, melphalan, prednisone was lower in the Programa para el Tratamiento de Hemopatías Malignas study of bortezomib, melphalan, prednisone versus bortezomib, thalidomide, prednisone [34] (Table 1), possibly associated with the use of only one versus four 6-week cycles of bi-weekly bortezomib dosing. Smaller studies of weekly regimens using higher doses of bortezomib (1.5–1.6 mg/m^2) have also reported a low incidence of BiPN.[95,96] Additionally, data from a randomized phase 3 trial[44] showed a significant reduction in overall, grade $\geqslant$2, and grade $\geqslant$3 BiPN with the use of subcutaneous versus intravenous administration of bortezomib in patients with relapsed MM. No loss of efficacy was seen and pharmacokinetic studies showed a reduction in C_{max} but not systemic exposure, as well as equivalent proteasome inhibition.[44]

The incidence and severity of TiPN is both dose- and duration-related, with actuarial incidence increasing over the course of treatment.[25] Although TiPN can occur after relatively short-term use (less than 20 g cumulative dose,[25] ~14 weeks at 200 mg/day), it generally occurs following chronic use over several months,[6,24,25,54,97] and has even been reported some time after treatment has been stopped.[24] Nonetheless, relatively low-dose, short-term thalidomide use has been shown to improve outcomes in the context of a double transplant protocol, and to be feasible, with limited rate of grade 3/4 TiPN (4%) and thalidomide discontinuation due to TiPN (2%).[98] Vincristine-induced PN is also associated with duration of exposure.[28]

Predisposing factors

In the phase 3 VISTA trial of bortezomib, melphalan, prednisone versus melphalan, prednisone in frontline MM, by multivariate analysis, a history of PN was the only consistent risk factor for any-grade, grade $\geqslant$2 and grade $\geqslant$3 BiPN; age, baseline diabetes, disease stage and creatinine clearance did not affect the incidence.[32] Consistent with these findings, in the APEX trial of bortezomib versus dexamethasone in relapsed/refractory MM, patients with baseline PN symptoms by FACT/GOG-Ntx assessment appeared to have a higher risk of grade $\geqslant$3 BiPN, but age, baseline glycosylated hemoglobin level and history of diabetes did not appear to affect the overall or grade 3/4 rates of BiPN.[43] Importantly, in the relapsed setting, prior therapy with known neurotoxic agents did not appear to affect the incidence of BiPN.[42,43,90,91]

Evaluations of possible predisposing factors of TiPN have reported conflicting results. In a study in relapsed/refractory MM patients, age, sex and prior therapy were not predictive of TiPN.[25] However, in the Total Therapy 2 study (in which patients received the neurotoxic agents thalidomide, vincristine and cisplatin), frontline patients aged $\geqslant$65 years had a higher incidence of TiPN than those aged $<$65 years.[99]

It has been postulated that parameters intrinsic to MM (for example, proinflammatory proteins and vascular mediators) may contribute to the emergence of PN and be reflected in primary tumor cell gene expression profiles. Recent results from the phase 3 Dutch-Belgian Cooperative Trial Group for Hematology Oncology and Intergroupe Francophone du Myelome trials have identified changes in gene expression profiles in MM plasma cells that were significantly associated with BiPN and vincristine-induced PN, as well as significantly associated single-nucleotide polymorphisms (SNPs).[100] By gene expression profiling, genes involved in drug-induced apoptosis, mitochondrial dysfunction and peripheral nervous system development were significantly associated with early-onset (within one cycle) BiPN, whereas peripheral blood analyses identified significant SNPs located in genes involved in cell death, DNA repair and the development and function of the nervous system.[100] Genes significantly associated with late-onset (cycles 2 and 3) BiPN again included those involved in nervous system development and function, and significant SNPs were identified in inflammatory genes and DNA repair genes. Vincristine-induced PN was associated with a different set of genes, suggesting that different molecular mechanisms are involved compared with BiPN. These findings suggest that both MM-related and inherent patient genetic variations contribute to the risk of BiPN.[100] Additionally, an independent pharmacogenomic analysis of whole blood samples from patients enrolled in the VISTA trial identified an association between time to onset of BiPN and the immune gene *CTLA4*.[101]

An analysis of the genetic factors that affect TiPN identified significant associations with SNPs in the ABC genes (*ABCC1*) and in neurological genes such as *SERPINB2*, indicating that TiPN may also be associated with neuro-inflammation and/or accumulation of damage or the inability to repair neuronal damage,[102] although the identified genes were distinct to those associated with BiPN. The same authors also analyzed the genetic factors that affect vincristine-induced PN and detected little overlap in the genes associated with TiPN and vincristine-induced PN.[102]

It is important to also highlight the possibility that different patient populations in different regions of the world may be affected differently in terms of treatment-emergent PN by the agents under discussion.

Reversibility

Although prolonged painful PN could adversely impact patient quality of life, BiPN is at least partially reversible in the majority of patients; for example, 60% of BiPN events completely resolved within a median of 5.7 months in VISTA,[32] and 64% of patients with grade $\geqslant$2 BiPN experienced improvement/resolution within a median of 3.6 months in APEX.[43] Similarly, in transplant-eligible patients who received induction with bortezomib, thalidomide, dexamethasone in a Gruppo Italiano Malattie EMatologiche dell'Adulto phase 3 trial, 78% of patients with grade 3/4 PN experienced improvement/resolution within a median of 26 days.[31] The reversibility of BiPN has also been demonstrated in preclinical neurophysiological and histological studies in a mouse model.[12,13] Such reversibility may contribute to the feasibility of bortezomib retreatment; [90,91] however, patients who experienced prior BiPN should be treated with caution.

There is mixed evidence for the reversibility of TiPN. In the Total Therapy 2 trial grade $\geqslant$2 PN improved to less than grade 2 within 3–4 months of stopping thalidomide in 90% of affected patients.[99] However, thalidomide is known to cause nerve damage that may be permanent,[24] and some studies have reported that TiPN may resolve slowly or not at all.[6,24]

Complete recovery of cisplatin-induced PN is only likely to occur several years after cisplatin discontinuation.[29]

Clinical recommendations

Clinical examples of PN cases commonly seen in MM patients are shown in Box 1. As discussed recently,[3] in the absence of curative therapy for treatment-emergent PN in MM, prevention is a key strategy for preserving quality of life and future treatment options. All MM patients who are to receive neurotoxic drugs should be clinically assessed for PN signs and symptoms before treatment initiation, particularly those with baseline PN, and throughout therapy. The use of dose modification for management of BiPN and TiPN remains the 'gold standard' of care.

Importance of early detection and monitoring

Regular monitoring for treatment-emergent PN and early detection and intervention are important to manage symptoms and prevent the development of more severe neuropathy,[4] ideally including assessment by the patient and/or oncology nurse with each dose of drug. This is particularly true for the small subgroup of patients who develop severe, early-onset BiPN (in APEX, 14 [4%] patients discontinued bortezomib because of grade $\geqslant 2$ BiPN within the first three cycles);[43] this may respond to high-dose corticosteroids and may be associated with viral infections. Clinical experience suggests that regular monitoring is also important post-transplantation in patients with prior PN as, in a small number of patients, PN symptoms may become relatively more problematic even several months post-transplant.

The NCI CTC definitions of PN are commonly used in the clinic (Table 3). These definitions may be more useful when used in conjunction with neuropathy-specific patient-completed questionnaires such as the FACT/GOG-Ntx,[103] the (reduced) Total neuropathy score,[42,104] the European Organisation for Research and Treatment of Cancer CIPN20 questionnaire,[105] and the CI-PERINOMS tool,[106] which may identify PN symptoms before adverse event reporting by physicians. However, none were developed specifically for MM, and each has limitations. Importantly, attempts to correlate patient-reported neuropathy using these tools with that reported by neurologist examination or clinical assessment have shown varying results. The reduced Total neuropathy score has been correlated with NCI CTC grading in some analyses,[104] but data from bortezomib studies in relapsed[42,43] and frontline[5] MM have not shown a correlation between neuropathy reported by neurologist examination, clinical assessment and patients using the FACT/GOG-Ntx questionnaire.

There remains a need for more sensitive, patient-focused PN assessment tools that specifically focus on the PN symptoms of MM patients. One suggestion is the development of a simple visual analog scale, similar to that used to assess pain in solid tumors,[107] with which patients could easily assess their current symptoms relative to a previous visit and any improvement or worsening of symptoms would be quickly detected.

Knowledge of predisposing factors may allow identification of patients at risk of PN; however, at present, there is little consistent evidence for predisposing factors, particularly in frontline MM. In addition, pharmacogenomic analysis may allow the development of a SNP classifier for predicting PN; further work is needed to determine the feasibility of this approach.

Neurological assessment in the management of treatment-emergent PN

Early neurological assessment, after each cycle of therapy, may be useful in the effective management of treatment-emergent PN in conjunction with more regular assessment by the treating physician, patient and oncology nurse. The incidence of PN has been shown to differ by clinical and neurologist assessment, with one study reporting a baseline clinical incidence of 20%, whereas 54% of patients who had a neurological assessment showed abnormal findings at diagnosis.[5] Early neurological assessment may therefore allow early identification of cases of treatment-emergent PN and neurological monitoring (using nerve conduction studies (NCS) and the reduced Total neuropathy score) has been shown to reduce the incidence of BiPN.[108] However, in contrast, another study in patients with relapsed/refractory MM who were treated with thalidomide indicated that careful clinical examination was better for monitoring PN than nerve electrophysiological studies.[25] Further studies are needed to determine whether action should be taken based on abnormal neurological findings alone.

Clinical assessment by a neurologist can be useful firstly in determining whether PN is treatment-emergent or MM-associated. Electromyograms (EMGs) may be useful in this respect because many MM-associated polyneuropathies are primarily demyelinating, whereas treatment-emergent PN is largely axonal. Second, a neurologist may reliably discern motor neuropathy from myopathy, which is mostly steroid-induced in MM patients. Third, clinical neurological assessment may accurately determine the severity of motor neuropathy, sensory neuropathy and neuralgia according to the NCI CTC criteria. Finally, a neurologist may start and monitor symptomatic treatment of PN using anti-epileptic or antidepressant medications. Such patients should be monitored until their pain is adequately controlled.

The value of NCS has been highlighted in cases of TiPN. Some electrophysiological studies have shown that patients with TiPN have decreased sensory nerve action potential amplitudes,[19,25,97] which has been suggested as the most sensitive parameter for detecting TiPN.[109] Consequently, assessment of peripheral nerve function has been proposed to manage TiPN. However, the procedures are more invasive than questionnaires and may not always reliably assess the severity of treatment-emergent PN; it has therefore been suggested that these procedures alone should not be used for diagnosis and treatment decisions, but may help to distinguish confounding cases in conjunction with other assessments.[6]

Treatment of treatment-emergent PN

Care should be taken when prescribing agents for the treatment of treatment-emergent PN as their use could result in continued dosing of neurotoxic MM therapy at the same intensity, which in turn could possibly cause permanent nerve damage because of prolonged treatment. Several interventions have been investigated for chemotherapy-induced PN, but none has yet been prospectively assessed in MM-specific PN or in combination with the agents discussed here. Commonly used approaches include anti-epileptic agents and antidepressants. Acetyl-L-carnitine has shown activity in the treatment of chemotherapy-induced PN.[110] Alpha-lipoic acid, which is approved in the European Union for treatment of diabetic neuropathy, has been shown to be effective against oxaliplatin-induced polyneuropathy in patients with advanced colorectal cancer.[111] Recently, double-blind, placebo-controlled studies have shown promising results with topical baclofen, amitriptyline and ketamine[112] in chemotherapy-induced PN, and with the antidepressant venlafaxine in colorectal cancer patients with oxaliplatin-induced PN.[113] Positive results have also been reported with topical menthol cream in a patient with bortezomib-induced neuropathic pain,[114] as well as with

Box 1 How do we manage our patients with PN?

Patient A

Patient A, a 70-year-old gentleman, was diagnosed with International Staging System stage I MM in 2008. The patient received melphalan–prednisone–lenalidomide. During treatment, his fasting glucose levels increased transiently, but the patient had no prior history of diabetes mellitus. Following melphalan–prednisone–lenalidomide withdrawal due to inadequate response, the patient received salvage therapy with eight cycles of bortezomib-dexamethasone. He achieved a very good partial response after seven cycles but started to complain of loss of feeling and numbness at the tips of both upper and lower extremities from the fifth cycle. He subsequently reported pain, primarily in the lower extremities, and sleeping became problematic; however, the symptoms did not interfere with his daily activities.

The patient was referred to a neurologist at the first appearance of symptoms and was monitored monthly thereafter. At the same time, he started to feel dizzy when suddenly standing. He had a history of constipation. The neurologist diagnosed grade 1 progressing to grade 2 peripheral and autonomic neuropathy. The patient was prescribed gabapentin 800 mg tid. Per dose-modification guidelines, the bortezomib dose was reduced to 1.0 mg/m^2. After symptomatic relief, the gabapentin dose was reduced to 400 mg bid after completion of bortezomib-dexamethasone. At the end of cycle eight, BiPN was re-evaluated as grade 1 and continues to improve. In all, 7 months after the start of neurological symptoms, the patient's main concern is residual but mild numbness on the underside of his feet. He has noticed a gradual, sustained improvement in his other neurological symptoms, confirmed by neurological examination. He is still receiving gabapentin 400 mg bid and remains in complete response (CR).

Patient B

Patient B, a 53-year-old gentleman, was diagnosed with International Staging System stage III MM in 2004. He achieved a CR with vincristine, doxorubicin, dexamethasone induction followed by high-dose melphalan and autologous stem cell transplantation (HDT-ASCT), without symptoms or signs suggestive of neuropathy. After symptomatic relapse in 2007, he received re-induction with bortezomib–dexamethasone. After four bortezomib infusions, the patient started to experience numbness in his feet, which rapidly progressed to a severe ataxia in both hands and feet, left him unable to walk, and severely affected dexterity. Within a few days he was unable to sit without support. The patient experienced dysesthesias in all four limbs, but did not consider these painful. On neurological examination a minimal quadriparesis of both proximal and distal muscles (Medical Research Council grade 4+) was present. Pinprick sensation was absent below the elbow and knee, vibration perception was absent below the elbows and pelvis. Tendon reflexes were absent in the arms and legs. By EMG examination, sural, median and ulnar sensory nerve potentials could not be evoked, whereas motor NCS were normal. Following immediate discontinuation of bortezomib, the patient gradually recovered and was able to walk without support within 6 months, and has since returned to good functional status. Following the abbreviated bortezomib-based treatment the patient was treated with dexamethasone alone for 6 months. At restaging he had achieved a stringent CR, which was ongoing in April 2010.

Patient C

Patient C, a 54-year-old gentleman, was diagnosed with International Staging System stage I MM in 2001. He received pamidronate, thalidomide and dexamethasone and achieved CR within 6 months. He then underwent HDT-ASCT, received thalidomide maintenance (100 mg daily) together with continued bisphosphonates, and remained in CR for the next 7 years. After ~1 year on thalidomide, he developed paresthesias in both feet. EMG examination and NCS suggested a small-fiber neuropathy. Over subsequent years, the paresthesias became more prominent, despite receiving nutritional supplements including alpha-lipoic acid, vitamin B complex and L-carnitine. Electrophysiological studies were consistent with a moderate, generalized, axonal and sensory polyneuropathy. Pregabalin was eventually added, and thalidomide dosing was reduced to 50 mg daily, leading to improvements in TiPN symptoms.

In early 2008, relapsed MM in his left proximal femur was proven on biopsy as well as recurrent disease in his thoracic spine and several other bony sites documented on PET/CT. He received radiation therapy to areas of symptomatic bone disease, followed by salvage induction with six 21-day cycles of lenalidomide, bortezomib, low-dose dexamethasone (RVd). His pain completely resolved and a follow-up PET/CT scan confirmed CR. The patient successfully underwent a second HDT-ASCT, after which his neuropathy worsened significantly, with symptoms beginning after high-dose cyclophosphamide was administered for stem cell mobilization. He developed a burning sensation, numbness and a sensation of coldness in his legs and feet, which worsened after re-engraftment and recovery. Neurological examination was notable for slight weakness of toe extensors, mild loss of sensation to cold and vibration distally in the lower extremities, and loss of ankle jerks. EMG and NCS analyses showed a generalized axonal sensory polyneuropathy. His symptoms were controlled with pregabalin 300 mg twice-daily and doxepin 25 mg at night. The use of emollients (cocoa butter, menthol-based cream) also proved helpful, together with regular therapeutic massage of his extremities. Nutritional supplements appeared to have some additional benefit and his BiPN improved to grade 1 (mild lower extremity hypoesthesia and paresthesia only).

Following sustained improvement in BiPN, he received two cycles of RVd. Full restaging confirmed sustained CR and his BiPN remained stable. The patient then received maintenance therapy with lenalidomide and weekly bortezomib 1.0 mg/m^2. He also continued on bisphosphonate infusion without complication. His BiPN remains mild (grade 1) and is not painful, with no limitations to his activities of daily living, and his symptoms are well controlled on low doses of pregabalin and doxepin. A total of 2 years after the second ASCT he remains in CR.

Commentary

The patients presented are from the United States, Europe and the Near East, showing the commonalities and differences in PN management according to international practice.

In the first case, following initial melphalan–prednisone–lenalidomide therapy, salvage therapy with bortezomib-based treatment resulted in a high quality response. Unfortunately, by the fifth cycle, PN began to emerge with symptoms typical of BiPN. Bortezomib dose reduction and the use of gabapentin provided symptomatic relief and allowed completion of the planned eight cycles of therapy. Importantly, the patient entered CR and, while requiring ongoing treatment for mild residual BiPN, he had a sustained neurological improvement, with no significant residual impact on his activities of daily living.

The second patient reflects an especially challenging presentation of BiPN in which after just one cycle of treatment a rapidly progressive and severe PN emerged, prompting discontinuation. Interestingly, although the sensory aspects were profound and ataxia was noted, EMG examination showed normal motor nerve conduction and confirmed marked sensory nerve dysfunction. In keeping with the reversibility of BiPN, the patient recovered
after cessation of bortezomib. His disease responded with dexamethasone, which may also have helped reverse at least the inflammatory component of BiPN.

The third patient represents initially an example of TiPN, demonstrating the cumulative nature of thalidomide-associated neurotoxicity. This proved manageable with pregabalin and dose reduction. Unfortunately, the patient's disease recurred, prompting salvage with RVd. Interestingly, BiPN with RVd was not a clinical feature until after cyclophosphamide administration. This relationship to alkylator exposure has been reported, and in this patient's case was also more apparent after HDT-ASCT. Comprehensive evaluation confirmed a generalized axonal sensory polyneuropathy. Use of both pregabalin and doxepin proved successful, as did the use of emollients and supplements. His BiPN improved over time and he was able to proceed to consolidation therapy with RVd. Maintenance followed, incorporating bortezomib on a weekly schedule and at reduced dose; conversely, he is tolerating lenalidomide at full dose without significant complication.

In summary, these three cases illustrate in detail the importance of a proactive, integrated approach to the management of treatment-emergent PN in MM. In all three patients, the successful outcomes reflect how through dose-reduction, schedule change and the rational use of combination therapies for MM as well as appropriate pharmacotherapy for PN, nutritional supplements and supportive care, this otherwise daunting and dose-limited complication can be successfully managed.

electro-acupuncture in lung and breast cancer patients.[115] No controlled comparative data are available in MM patients; treatment remains empiric.

Prophylaxis

On the basis of trials and anecdotal evidence in MM, potential PN prophylaxis in MM patients could include: vitamin supplements, including multi-B complex with B1, B6 and B12, folic acid and vitamin E; magnesium supplement; increased dietary potassium intake; amino acid supplements, fish oils, omega-3 fatty acids, evening primrose oil, and flax seed oil; medications as indicated, including gabapentin, pregabalin, amitriptyline and duloxetine; and topical creams such as cocoa butter.[5] Daily vitamins, gabapentin and nortryptiline have been combined in a step-wise cocktail for frontline MM patients experiencing grade $\geqslant 1$ PN or neuropathic pain treated at the Dana–Farber Cancer Institute (Supplementary Table 2).[5] There remains a need for prospective evaluation of the effects of these interventions in the prevention of PN specifically associated with different MM therapies. Additionally, neuro-rehabilitation through physical and occupational therapy might be considered for prospective evaluation in patients developing TiPN or BiPN.

Agent-specific recommendations for PN management

Although the choice of MM agent for each individual patient is based on many factors, it is important that the burden of MM-associated PN be considered together with that of treatment-emergent PN; MM agents that induce rapid and durable responses may also reduce the burden of MM-associated PN.

Bortezomib. On the basis of experience in phase 2 studies, evidence-based dose-modification guidelines were developed for the management of BiPN and are included in the prescribing information for bortezomib (Table 4).[43] Table 4A reflects existing guidelines. Table 4B is a recommended approach generated by consensus for combination regimens. Early monitoring and prompt use of these evidence-based dose-modification guidelines have been shown to lead to improvement or resolution of BiPN, while maintaining therapeutic efficacy,[43] and these guidelines should be used routinely. Use of weekly bortezomib dosing in combination regimens might be an effective dose-modification strategy for grade 1 BiPN, but further research is needed to determine how this might be integrated into the current guidelines.

The reversibility of BiPN in a substantial proportion of patients has been repeatedly demonstrated.[5,32,42,43,94,116] Patients with prior BiPN are not necessarily precluded from receiving subsequent bortezomib-based therapy, although such patients should be treated with appropriate caution. One possible approach would be to commence retreatment with bortezomib using a lower dose or a once-weekly schedule, with subsequent escalation if tolerated.

Additionally, recent data[44] showing a substantial reduction in BiPN with subcutaneous versus intravenous administration of bortezomib highlights the potential importance of regimens utilizing subcutaneous bortezomib for minimizing the incidence of BiPN.

Thalidomide. Dose modification and discontinuation should also be used for TiPN. As suggested recently,[117] in clinical practice, thalidomide is often dose-reduced in cases of grade 2 TiPN and discontinued for grade $\geqslant 3$ TiPN, with resumption of dosing if TiPN improves to grade 1. However, there remains a need for a validated dose-modification guideline for TiPN. On the basis of available data, it has been suggested that thalidomide be limited to <200 mg/day to minimize TiPN and should be dose-reduced or discontinued in patients with grade 2 or 3 TiPN, respectively.[118] We recommend that thalidomide be discontinued once grade 2 TiPN occurs, and restarted with a 50% dose reduction upon resolution to grade $\leqslant 1$ if the risk-benefit ratio is favorable.[3] Additionally, patients with grade 1 TiPN should have their thalidomide dose reduced by 50%.[3] Dose modification and discontinuation can also be used to reduce the risk of TiPN evolving. For example, during maintenance treatment, the thalidomide dose could be reduced to 50 mg/day as soon as a patient has achieved a plateau response. Some studies have suggested that thalidomide use should be limited to 6 months,[25] although prolonged use, limited to 6–12 months, may be feasible if low doses are administered.

Conclusions and future directions

In the absence of effective prophylaxis, the aim is to manage treatment-emergent PN while maintaining therapeutic efficacy. Many studies have characterized BiPN, leading to the development of strategies that allow many cases of BiPN to be managed effectively and to resolve in the majority of patients. Strategies for BiPN management include early and regular monitoring by clinical and neurological evaluation and patient-reported questionnaires, and prompt dose modification and discontinuation, using evidence-based guidelines. Additionally, use of subcutaneous versus intravenous administration is a potentially important new strategy.

Further studies, particularly on TiPN, are needed to improve PN management in MM patients. There is also a need for further investigation of PN with combination therapies. The etiology, incidence and severity of PN with investigational agents, including newer proteasome inhibitors and immunomodulators, also require more research. To identify patients most at risk, further assessment of predisposing factors and pharmacogenomic markers of PN is warranted. MM-specific patient-focused PN assessment tools should also be developed to ensure early identification and consistent monitoring of PN. Finally, the MM-specific benefits of pharmacological interventions for treatment-emergent PN should be prospectively assessed. Such developments should allow further optimization of PN management and the development of effective prophylaxis strategies.

Conflict of interest

Paul G Richardson is an advisor for Millennium Pharmaceuticals, Celgene Corporation, Novartis Pharmaceuticals, Johnson & Johnson and Bristol Myers Squibb. Michel Delforge is a consultant for Janssen and Celgene. He has also received speaker's honoraria from these companies. Joost L Jongen has received personal compensation from Pfizer. Orhan Sezer has received honoraria from Amgen, Celgene, Janssen and Novartis. Dr Sezer has also received research funding from Janssen and Novartis. Antonio Palumbo has received honoraria from Celgene, Janssen-Cilag, Merck and Amgen, and is on an advisory committee for Celgene and Janssen-Cilag. Shaji Kumar has received research funding from Celgene, Millennium and Novartis. He is a consultant for Merck. Philippe Moreau has received honoraria from Celgene, Janssen and Millennium. Michele Cavo has received honoraria from Janssen, Celgene and Millennium. Peter Voorhees is on speaker bureaus for Celgene

Table 4 Currently recommended (A) and new proposed (B) dose-modification guidelines for bortezomib-related neuropathic pain and/or peripheral sensory or motor neuropathy

(A) Currently recommended dose-modification guideline for bortezomib-related neuropathic pain and/or peripheral sensory or motor neuropathy[23]

Severity of peripheral neuropathy signs and symptoms	*Modification of bortezomib dose and regimen*
Grade 1 (paresthesias, weakness and/or loss of reflexes) without pain or loss of function	No action
Grade 1 with pain or Grade 2 (interfering with function, but not with activities of daily living)	Reduce bortezomib dose to 1.0 mg/m^2
Grade 2 with pain or Grade 3 (interfering with activities of daily living)	Withhold treatment until toxicity resolves. When toxicity resolves, reinitiate with a reduced dose of bortezomib at 0.7 mg/m^2 and change treatment schedule to once per week
Grade 4 (sensory neuropathy that is disabling or motor neuropathy that is life-threatening or leads to paralysis)	Discontinue bortezomib

(B) New proposed dose-modification guideline (see text for discussion)[3]

Severity of peripheral neuropathy signs and symptoms	*Modification of bortezomib dose and regimen*	*Supportive data*
Grade 1 (paresthesias, weakness and/or loss of reflexes) without pain or loss of function	Reduce current bortezomib dose by one level (1.3 → 1.0 → 0.7 mg/m^2) Or, for patients receiving a twice-weekly schedule, change to a once-per-week schedule using the same dose Consider starting with 1.3 mg/m^2 once per week in patients with history of prior peripheral neuropathy	Prior peripheral neuropathy was the only risk factor associated with bortezomib-related peripheral neuropathy in newly diagnosed patients treated with VMP[32] Baseline peripheral neuropathy was a risk factor for development bortezomib-related peripheral neuropathy of grade $\geqslant$3 in relapsed/refractory MM patients treated with single-agent bortezomib[42] A VMP regimen using bortezomib 1.3 mg/m^2 once weekly from the start of therapy showed reduced neurotoxicity and delivered a similar cumulative dose of bortezomib to that in VISTA, and resulted in similar efficacy[30]
Grade 1 with pain or Grade 2 (with no pain, but limiting instrumental activities of daily living)	For patients receiving twice-weekly bortezomib, reduce current dose by one level, or change to a once-per-week schedule using the same dose. For patients receiving bortezomib on a once-per-week schedule: reduce current dose by one level, OR consider temporary discontinuation; upon resolution (grade $\leqslant$1), restart once-per-week dosing at lower dose level in cases of favorable benefit-to-risk ratio	Early reduction of bortezomib from 1.3 mg/m^2 twice weekly to once weekly in patients receiving VMP showed reduced neurotoxicity, delivered similar cumulative dose of bortezomib to that in VISTA, and resulted in similar efficacy[34] Dose-reduction strategies including dose reduction from 1.3 to 1.0 mg/m^2, changing from twice-weekly to once-weekly dosing, and withholding of bortezomib resulted in improvement or resolution of peripheral neuropathy in most patients with bortezomib-related peripheral neuropathy[32,43]
Grade 2 with pain, Grade 3 (limiting self care and activities of daily living), or Grade 4	Discontinue bortezomib	Discontinuation as part of a peripheral neuropathy management strategy resulted in improvement or resolution of clinically significant neuropathy in 71% of patients in an analysis of two phase 2 studies of bortezomib[42]

Abbreviations: MM, multiple myeloma; VMP, bortezomib, melphalan–prednisone.
In part A, grading for this currently recommended dose-modification guideline is based on National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 3.0. In APEX, the dose-modification guideline used was the same, but based on NCI CTC version 2.0 grading; in addition, patients experiencing grade 3 peripheral neuropathy with pain were to discontinue bortezomib.
In part B, a for part A, grading is based on NCI CTCAE v3.0.

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Supplementary Information accompanies the paper on the Leukemia website (http://www.nature.com/leu)