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ORIGINAL REPORT

Frequency, Characteristics, and Reversibility of Peripheral Neuropathy During Treatment of Advanced Multiple Myeloma With Bortezomib

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ABSTRACT

Purpose
To determine the frequency, characteristics, and reversibility of peripheral neuropathy from bortezomib treatment of advanced multiple myeloma.

Patients and Methods
Peripheral neuropathy was assessed in two phase II studies in 256 patients with relapsed and/or refractory myeloma treated with bortezomib 1.0 or 1.3 mg/m^2 intravenous bolus on days 1, 4, 8, and 11, every 21 days, for up to eight cycles. Peripheral neuropathy was evaluated at baseline, during the study, and after the study by patient-reported symptoms using the Functional Assessment of Cancer Therapy Scale/Gynecologic Oncology Group–Neurotoxicity (FACT/GOG-Ntx) questionnaire and neurologic examination. During the study, peripheral neuropathy was also evaluated by investigator assessment. A subset of patients underwent nerve conduction studies (n = 13).

Results
Before treatment, 194 (81%) of 239 patients had peripheral neuropathy by FACT/GOG-Ntx questionnaire, and 203 (83%) of 244 patients had peripheral neuropathy by neurologic examination. Treatment-emergent neuropathy was reported in 35% of patients, including 37% (84 of 228 patients) receiving bortezomib 1.3 mg/m^2 and 21% (six of 28 patients) receiving bortezomib 1.0 mg/m^2. Grade 1 or 2, 3, and 4 neuropathy occurred in 22%, 13%, and 0.4% of patients, respectively. The incidence of grade ≥ 3 neuropathy was higher among patients with baseline neuropathy by FACT/GOG-Ntx questionnaire compared with patients without baseline neuropathy (14% *v* 4%, respectively). In all 256 patients, neuropathy led to dose reduction in 12% and discontinuation in 5%. Of 35 patients with neuropathy ≥ grade 3 and/or requiring discontinuation, resolution to baseline or improvement occurred in 71%.

Conclusion
Bortezomib-associated peripheral neuropathy seemed reversible in the majority of patients after dose reduction or discontinuation. Although severe neuropathy was more frequent in the presence of baseline neuropathy, the overall occurrence was independent of baseline neuropathy or type of prior therapy.

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INTRODUCTION

Peripheral neuropathy is a major dose-limiting adverse effect of many anticancer agents. In patients with multiple myeloma, peripheral neuropathy is not only associated with the agents used to treat the disease, such as bortezomib,[1,2] thalidomide,[3] and vincristine,[4] but it is also associated with the disease itself.[5]

Bortezomib has demonstrated activity and safety in heavily pretreated patients with relapsed and/or refractory multiple myeloma in phase II and III trials.[1,2,6] The most frequent adverse events reported with bortezomib include GI symptoms, fatigue, cyclical thrombocytopenia, and peripheral neuropathy.[1,2,6,7] Peripheral neuropathy was first reported in phase I trials.[8-10] In the development of the multicenter, prospective, phase II Study of Uncontrolled Multiple Myeloma Managed with Proteasome Inhibition Therapy (SUMMIT)[1] and Clinical Response and Efficacy Study of Bortezomib in the Treatment of Relapsing Multiple Myeloma (CREST)[2] trials, the

protocols incorporated special assessments for neuropathy and mandated the involvement of a neurologist at each study center.

The objectives of this analysis were to evaluate the frequency, characteristics, and reversibility of peripheral neuropathy in patients with relapsed and/or refractory myeloma treated with bortezomib who participated in SUMMIT and CREST. To accomplish these objectives, multiple methods were used including patient-reported outcomes, examination by a neurologist, investigator assessments, and, at one center, nerve conduction studies.

PATIENTS AND METHODS

The eligibility criteria for the patients enrolled onto SUMMIT and CREST have been described previously.[1,2] Eligible patients had relapsed and/or refractory myeloma; patients with polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes syndrome (POEMS) were excluded, but otherwise, there were no exclusions specified for the presence of peripheral neuropathy.

All patients provided written informed consent before study enrollment. These studies were conducted in accordance with the Declaration of Helsinki; each participating study center obtained institutional review board approval.

Treatment and Study Design

The SUMMIT and CREST trials were open-label, multicenter studies in which patients received bortezomib 1.3 mg/m^2 and 1.0 or 1.3 mg/m^2, respectively, by intravenous bolus on days 1, 4, 8, and 11 of a 21-day cycle. If patients had progressive disease after two cycles or stable disease after the first four cycles, they were eligible to receive oral dexamethasone 20 mg on the day of and day after bortezomib treatment. Patients could receive up to eight cycles, and patients who continued to benefit from treatment or had the potential to benefit were eligible to receive treatment in an extension study.[1,2,8]

Adverse events were assessed and reported by the investigator at each visit. Toxicity was graded using the National Cancer Institute Common Toxicity Criteria (NCI CTC), version 2.0. Any grade 3 or 4 nonhematologic toxicity required that bortezomib be held for up to 2 weeks until the toxicity returned to grade 1. When treatment was resumed, the bortezomib dose was reduced by 25%. Patients who developed signs and/or symptoms of peripheral neuropathy were treated symptomatically. There was no specific guidance for dose modification or treatment in the event of peripheral neuropathy given in these protocols.

Neurologic Assessments

Baseline status of the patients was obtained from a patient-completed questionnaire for neurologic toxicities (Functional Assessment of Cancer Therapy Scale/Gynecologic Oncology Group–Neurotoxicity [FACT/GOG-Ntx]), neurologic questioning and examination by a consulting neurologist, and electrophysiologic testing at one participating center. The FACT/GOG-Ntx questionnaire[11] was administered at screening, on day 1 of cycles 3, 5, and 7, and at study end.

Patients were assessed by a neurologist for neuropathic symptoms and signs during the study period using a modified version of a standard assessment used in some other studies.[10,12] At the investigator's discretion, the neurologic evaluation could be repeated during therapy and at the end of the study. This evaluation included specific questions regarding symptoms (sensory, autonomic, motor, and changes) and functional impairment and was essentially a modification of the Neuropathy Symptom Score and Neuropathy Symptoms and Change Score used in other studies.[13,14] Muscle strength, sensation (light touch, pain, vibration, and proprioception), deep tendon reflexes, and blood pressure were assessed. The sensory, motor symptom, and examination scores and the autonomic score were used to calculate a total neuropathy score.

Treatment-emergent neuropathy was also evaluated by the investigator; however, baseline investigator assessments by NCI CTC grade were not collected. An algorithm using specific components of the FACT/GOG-Ntx questionnaire and neurologic examination was developed to derive the baseline NCI CTC grade. A subgroup of patients from the lead study center underwent motor and sensory nerve conduction studies and quantitative sensory testing of vibratory, heat, and cold perception at baseline; during cycles 3, 5, and 7; at study completion; and as needed in patients who developed signs or symptoms of neuropathy during the study.[14,15]

Statistical Analysis

The number of observations, mean, standard deviation, median, minimum, and maximum for continuous variables and the number and percentage for categoric data were calculated. The estimated probability of first onset of peripheral neuropathy was determined using the Kaplan-Meier method. All analyses were produced using SAS software (Version 8.2; SAS Institute, Cary, NC). The Wilcoxon signed rank test was used to assess change in total neuropathy scores, subscores, FACT/GOG-Ntx scores, and the nerve conduction data from baseline to study completion. The Wilcoxon rank sum test was used to assess differences between patients who developed symptomatic neuropathy and patients who did not.

RESULTS

Baseline Peripheral Neuropathy

Baseline characteristics of the 256 patients treated with bortezomib in the two phase II studies are listed in Table 1. The proportion of patients with symptoms of peripheral neuropathy at baseline was 81% (194 of 239 patients) by FACT/GOG-Ntx questionnaire and

Table 1. Baseline Characteristics

Characteristic	No. of Patients (N = 256)	%
Age, years		
Median	60	
Range	30-84	
Sex		
Female	112	44
Male	144	56
History of diabetes	29	11
Baseline FACT/GOG-Ntx*	239	
Symptoms of peripheral neuropathy†	194	81
Neurologic examination‡	244	
Sensory or motor symptoms and signs	203	83
Functional impairment with sensory or motor symptoms and signs	116	48
Peripheral neuropathy§	252	
Stage 0: normal	60	24
Stage 1: loss of deep tendon reflexes or paresthesias	60	24
Stage 2: objective sensory loss or paresthesia interfering with function	110	44
Stage 3: sensory loss or paresthesia interfering with ADL	22	9
Prior neurotoxic therapy	256	
Vincristine based	192	75
Thalidomide	184	72
Platinum	92	36

Abbreviations: ADL, activities of daily living; FACT/GOG-Ntx, Functional Assessment of Cancer Therapy Scale/Gynecologic Oncology Group-Neurotoxicity.
*Baseline data for FACT/GOG-Ntx available from 239 of 256 patients.
†Defined as a score greater than 0 on questions Ntx 1 to Ntx 4, Ntx 8, or Ntx 9 on FACT/GOG-Ntx (version 4).
‡Baseline neurologic evaluations performed by a neurologist in 244 of 256 patients.
§Based on a scoring method using specific components of the FACT/GOG-Ntx questionnaire and neurologic examination; baseline data from both tools available for 252 of 256 patients.

Table 2. Total Neuropathy Scores, Subscores of Its Major Individual Components As Graded by Examining Neurologists, and FACT/GOG-Ntx Summary Scores

	Neurologist Assessment of Patients																				FACT/GOG-Ntx Summary Score (Max 44)			
	Motor Symptom Score (Max 20)				Motor Examination Score (Max 34)				Sensory Symptom Score (Max 24)				Sensory Examination Score (Max 66)				Autonomic Score (Max 6)				Total Neuropathy Score† (Max 150)							
Neuropathy	No.	Median	Range	*P**	No.	Median	Range	*P**	No.	Median	Range	*P**	No.	Median	Range	*P**	No.	Median	Range	*P**	No.	Median	Range	*P**	No. of Patients	Median	Range	*P**
Baseline				.1234				.8815				.2721				.0040				.8234				.0046				.1440
All patients	237	0	0-19		236	0	0-34		240	0	0-24		242	9.0	0-36		223	1.0	0-6		243	15.0	0-95.6		239	9.0	0-39	
No neuropathy	151	0	0-16		150	0	0-34		154	2.0	0-24		155	8.0	0-36		141	1.0	0-6		156	14.0	0-95.6		153	7.0	0-34	
Treatment-emergent neuropathy	86	1.1	0-19		86	0	0-22		86	2.0	0-23		87	12.0	0-34		82	1.0	0-5		87	20.2	0-70		86	11.0	0-39	
End of study				.0093				.0450				< .0001				.0004				.4204				< .0001				.0005
All patients	104	4.0	0-18		107	0	0-34		104	5.5	0-24		110	17.3	0-40		101	2.0	0-6		111	32.0	0-77		188	12.0	0-38	
No neuropathy	49	2.0	0-16		50	0	0-34		50	3.0	0-17		53	13.0	0-33		48	1.8	0-4.5		53	22.0	0-72		110	10.0	0-35	
Treatment-emergent neuropathy	55	5.0	0-18		57	2.0	0-24		54	8.5	0-24		57	21.0	4-40		53	2.0	0-6		58	38.5	2.8-77		78	15.0	0-38	

NOTE. Higher values denote poorer function.
Abbreviations: FACT/GOG-Ntx, Functional Assessment of Cancer Therapy Scale/Gynecologic Oncology Group–Neurotoxicity; Max, maximum score for each subscale; SD, standard deviation.
*Comparison between values for patients with and without treatment-emergent neuropathy.
†Individual scores are tallied to arrive at a total neuropathy score.

83% (203 of 244 patients) by the neurologists' examinations. Table 2 lists the baseline and end-of-study neuropathy scores and subscores, as assessed by neurologists and by the FACT/GOG-Ntx questionnaire. The baseline FACT/GOG-Ntx scores were similar among patients who had treatment-emergent neuropathy and those who did not. However, there were statistically significant differences in the baseline total neuropathy and sensory examination scores from the neurologist among patients who developed treatment-emergent neuropathy and those who did not; the differences for other subscores were not statistically significant.

Twenty-two patients (9%) had FACT/GOG-Ntx scores and neurologist scoring at baseline that were equivalent to NCI CTC grade 3 neuropathy. The mean baseline FACT/GOG-Ntx summary score for these patients was 21.3 compared with 10.3 for all patients (of a maximum score of 44 on this test). The mean sensory neurologic examination score for these 22 patients at baseline was 10.1 compared with 11.0 in all patients. Thus, there was an apparent dissociation between subjective symptom and objective examination scores for patients with significant baseline sensory neuropathy.

Frequency and Severity of Peripheral Neuropathy During Treatment

Overall, investigators reported that 35% of patients (90 of 256 patients) had evidence of treatment-emergent peripheral neuropathy of any NCI CTC grade or worsening of baseline neuropathy. Patients with and without neuropathy at baseline based on the FACT/GOG-Ntx questionnaire had similar frequencies of treatment-emergent neuropathy (36% for each patient group). Grade 3 peripheral neuropathy tended to be more frequent in patients with evidence of peripheral neuropathy at baseline by FACT/GOG-Ntx questionnaire compared with patients without baseline evidence of peripheral neuropathy (14% *v* 4%, respectively; $P = .08$).

After treatment, the median FACT/GOG-Ntx scores were significantly higher whether treatment-emergent neuropathy was reported ($P < .0001$) or not ($P = .0002$). In addition, from baseline to the study end, a statistically significant increase in the total neuropathy score by neurologist assessment ($P \leq .0001$) and all subscores (range, $P < .0001$ to .0207), was observed for the entire patient population and for patients with or without treatment-emergent neuropathy, except the motor examination score in patients without treatment-emergent neuropathy. Thus, increased neuropathy scores in patients not experiencing painful neuropathy suggest that some had a subclinically evolving neuropathy.

Treatment-emergent peripheral neuropathy was 21% in patients receiving bortezomib 1.0 mg/m^2 and 37% in patients receiving bortezomib 1.3 mg/m^2 (Table 3). As the cumulative bortezomib dose increased, the prevalence of peripheral neuropathy increased, reaching a plateau at cycle 5 (approximately 30 mg/m^2 cumulative dose) and remaining fairly consistent through cycle 8. There was a positive correlation between cumulative bortezomib dose and FACT/GOG-Ntx summary score ($r = 0.108$; $P = .0037$) and total neuropathy score ($r = 0.297$; $P < .0001$). The analysis according to age or prior thalidomide, vincristine, or platinum treatment did not show any apparent relationship to the incidence of treatment-emergent peripheral neuropathy.

Nerve conduction studies and quantitative sensory testing were available in 13 patients. Six of 13 patients had evidence of a generalized

Table 3. Treatment-Emergent Peripheral Neuropathy by Dose and Grade

	Bortezomib 1.0 mg/m^2 (n = 28)		Bortezomib 1.3 mg/m^2 (n = 228)	
Grade	No. of Patients	%	No. of Patients	%
Grade 1	3	11	16	7
Grade 2	1	4	37	16
Grade 3	1	4	31	14
Grade 4	1	4	0	0
Total	6	21	84	37

NOTE. Grade assigned by the investigator according to National Cancer Institute Common Toxicity Criteria version 2.0.

axonal sensorimotor polyneuropathy at baseline. Consistent with other assessments, there was no significant difference at baseline between patients who developed treatment-emergent neuropathy or worsening neuropathy and patients who did not (Table 4). There was no significant difference in any nerve conduction study parameter at the end of the study compared with baseline examinations, although there was a trend toward reduced amplitudes of the sural sensory nerve action potentials in patients who developed treatment-emergent neuropathy and in the ulnar sensory nerve action potential but not in any motor action potentials (Fig 1, Table 4). Of the seven patients without electrophysiologic evidence of a large-fiber polyneuropathy at baseline, three developed symptomatic treatment-emergent small-fiber neuropathy (characterized by burning aching pain, paresthesia, and allodynia) during the study without significant changes seen on nerve conduction studies.

Outcomes, Interventions, and Reversibility

Of 90 patients with treatment-emergent peripheral neuropathy, 35 experienced ≥ 3 neuropathy and/or neuropathy leading to discontinuation. Peripheral neuropathy was the reason for discontinuing treatment in 5% of patients (14 of 256 patients), representing 16% of patients (14 of 90 patients) who developed new or worsening neuropathy. Of the 14 patients who discontinued treatment, eight experienced onset of neuropathy during the first three cycles. When treatment was discontinued, peripheral neuropathy was grade 4 in one patient, grade 3 in 11 patients, and grade 2 in two patients. Dose reduction was required in 12% of patients (31 of 256 patients) because of peripheral neuropathy, representing 34% of patients (31 of 90 patients) who developed new or worsening neuropathy. At least one dose of bortezomib was held because of peripheral neuropathy in 7% of patients (19 of 256 patients), representing 21% of patients (19 of 90 patients) with new or worsening neuropathy.

Neuropathic pain and other symptoms resolved to baseline levels or improved in 71% of patients (25 of 35 patients) with clinically significant neuropathy based on data at last follow-up. Resolution or improvement occurred during treatment in 37% of patients (13 of 35 patients) and after treatment in 31% of patients (11 of 35 patients). In one patient, it was unclear whether improvement occurred during or after treatment. Ten patients did not experience improvement in painful peripheral neuropathy after the final dose of bortezomib, but follow-up was limited because of progressive myeloma that was rapidly fatal in five patients. The median duration from the last dose to resolution or improvement of peripheral neuropathy was 47 days (range, 1 to 529 days).

Medications commonly administered for the treatment of peripheral neuropathy were recorded as gabapentin, vitamin and nutritional supplements (eg, vitamin B_6, alpha lipoic acid, and glutamine), opioids (eg, oxycodone, hydrocodone, fentanyl, and morphine), antidepressants (eg, amitriptyline, nortriptyline, and desipramine), and nonsteroidal anti-inflammatory agents (eg, celecoxib, rofecoxib, and ibuprofen).

DISCUSSION

Bortezomib-associated peripheral sensory neuropathy was first observed in phase I studies.[8-10] As a result, a concerted effort was made to accurately assess peripheral neuropathy in the phase II SUMMIT[1] and CREST[2] trials. Because there is no commonly accepted standard for assessment of peripheral neuropathy, multiple methods, including patient-reported outcomes, investigator assessments, and neurologists' examinations, were used. The patient questionnaire was easiest to use for assessment, and slightly more peripheral neuropathy events were reported using this method. This finding is aligned with improved sensitivity of patient versus investigator reporting of adverse events described in other studies.[16]

Results from this analysis demonstrated that peripheral neuropathy associated with bortezomib seems to be a cumulative,

Table 4. Sensory Nerve and Compound Muscle Action Potential Amplitudes at Baseline Compared With End of Study

	All Patients (n = 13)		Treatment-Emergent Neuropathy (n = 7)		No Treatment-Emergent Neuropathy (n = 6)	
Amplitude	Baseline	EOS	Baseline	EOS	Baseline	EOS
Sural sensory, μV*						
Mean	5.0	3.4†	4.8†	1.9†	5.4	5.0
SD	5.4	3.7	5.0	2.4	6.3	3.0
Range	0-16	0-10.3	0-14.5	0-5.1	0-16	0-10.3
Ulnar sensory, μV‡						
Mean	13.6	11.4	11.0	9.3†	16.5	14.0
SD	8.6	6.4	6.6	4.1	10.2	8.0
Range	0-26	0-22	1.9-21.4	4.7-16.9	0-26	0-22
Peroneal motor, μV§						
Mean	3.8	3.4	3.7	3.3	4.0	3.6
SD	2.0	1.7	1.7	1.3	6.9	5.9
Range	1-8	0.9-6.5	2.1-5.7	2.2-5.4	1-8	0.9-6.5
Ulnar motor, μV§						
Mean	8.6	8.7	9.2	9.3	8.0	8.0
SD	6.7	3.7	12.3	4.7	1.1	2.3
Range	5.3-15.6	6-13.2	5.3-15.6	6.1-13.2	6.7-9.1	6-10.5

NOTE. No changes reached significance ($P < .05$).
Abbreviations: EOS, end of study; SD, standard deviation.
*Normal > 5 μV.
†Abnormal.
‡Normal > 10 μV.
§Normal > 2 μV.

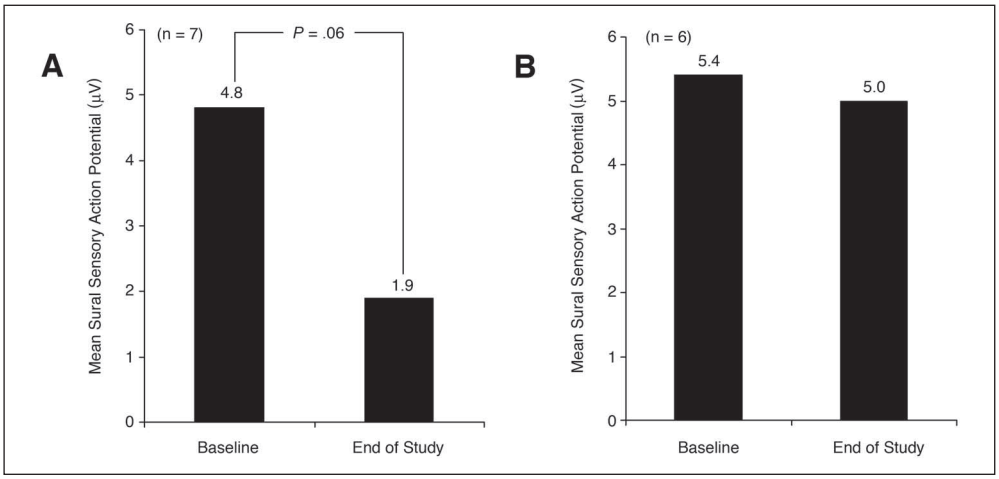

Fig 1. Mean sural sensory action potential amplitudes at baseline and end of study among patients who (A) did or (B) did not develop treatment-emergent sensory neuropathy.

dose-related adverse effect that increases in prevalence through the first five treatment cycles. Most patients (71%) with clinically significant neuropathy experienced resolution or improvement of neuropathic pain and other symptoms during treatment after dose modification or on completion of therapy. An additional 14% of patients died before first follow-up, indicating that the rate of resolution or improvement may have been higher. Importantly, among patients who were treated in an extension trial to the SUMMIT and CREST studies, prolonged bortezomib exposure did not seem to increase the incidence or severity of treatment-emergent peripheral neuropathy.[11]

In this study, there tended to be a higher incidence of grade 3 or 4 neuropathy in patients with baseline evidence of neuropathy by FACT/GOG-Ntx ($P = .08$). However, the overall rate of treatment-emergent peripheral neuropathy during bortezomib treatment could not be predicted from baseline total neuropathy or FACT/GOG-Ntx questionnaire scores. Importantly, sensory neuropathic symptoms may be out of proportion to objectively measurable signs at baseline and were also noted during treatment in three patients in whom nerve conduction studies and quantitative sensory testing showed no change, a phenomenon which is typical of small-fiber involvement. Therefore, patient history and symptomatic enquiry may be especially helpful in not only predicting potential risk but also in assessing patients during therapy.

In this analysis, the development of treatment-emergent peripheral neuropathy seemed to be independent of the type of prior neurotoxic therapy that the patient received. Recent reports illustrate that bortezomib can be combined with other agents that are neurotoxic such as thalidomide.[17] In front-line myeloma trials of bortezomib at the same dose and schedule (but for fewer cycles) combined with dexamethasone and administered with or without doxorubicin, low-grade neuropathy was reported in a comparable or higher proportion of patients, but high-grade neuropathy and neuropathy resulting in discontinuation of treatment were less common, with improvement or resolution reported in most patients.[18,19]

At present, dose modification guidelines are warranted (Table 5). Adherence to these recommendations in the Assessment of Proteasome Inhibition for Extending Remissions (APEX) trial[6,20] may have contributed to a reduction in grade ≥ 3 peripheral neuropathy compared with the findings of SUMMIT[1] and CREST,[2] although this cannot be verified on these data alone.

Given that bortezomib represents an active treatment providing durable responses and a survival advantage in relapsed myeloma, its benefits are clear.[6] As alluded to earlier, patients should be monitored for emergence of new or worsening symptoms or signs of neuropathy during treatment. Patient-completed questionnaires, such as the FACT/GOG-Ntx, may be helpful tools to identify patients at risk early and to institute dose-modification guidelines. Future studies to better characterize peripheral neuropathy in newly diagnosed patients and prospective evaluations of potential interventions to improve patient outcome are ongoing. Reliable assessment and management of neuropathy, with its significant impact on quality of life, constitutes an increasingly important component in the care of patients with multiple myeloma.

Table 5. Recommended Dose Modification for Peripheral Neuropathy

Severity of Peripheral Neuropathy	Modification of Dose and Schedule
Grade 1 (paresthesias or loss of reflexes) without pain or loss of function	No action
Grade 1 with pain or grade 2 (interferes with function but not with ADL)	Reduce to 1.0 mg/m^2
Grade 2 with pain or grade 3 (interferes with ADL)	Withhold treatment until toxicity resolves, then reinitiate at a dose of 0.7 mg/m^2 once weekly
Grade 4 (permanent sensory loss that interferes with function)	Discontinue treatment

Abbreviation: ADL, activities of daily living.

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Although all authors completed the disclosure declaration, the following authors or their immediate family members indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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