Peripheral neuropathy and new treatments for multiple myeloma: background and practical recommendations

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ABSTRACT

In multiple myeloma, peripheral neuropathy has for a long time been considered as mainly secondary to the plasma cell dyscrasia itself. With the advent of new targeted drugs such as thalidomide and bortezomib, the iatrogenic neurotoxicity has become the leading cause of peripheral neuropathy. This review discusses the pathogenesis, incidence, risk factors, diagnosis, characteristics, and management of peripheral neuropathy related to new multiple myeloma drugs, mainly bortezomib and thalidomide. The current knowledge of the pathophysiology of the new forms of peripheral neuropathy is still limited. The mechanisms involved depend on the agents used, patient's medical history, and duration of exposure and/or treatment doses or sequence. Diagnosis of such peripheral neuropathy is often easier than treatment. A full anamnesis and regular clinical evaluation are necessary. Electrophysiological assessments may support the diagnosis, although their contribution remains insufficient. Complex clinical features may require a specialized neurological assessment within the context of a multi-disciplinary approach. Finally, early detection of peripheral neuropathy and the use of dose adjustment algorithms as in the case of bortezomib, should help reduce the side effects while maintaining anti-tumor efficacy.

Key words: peripheral neuropathy, multiple myeloma, practical recommendations.

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Introduction

In multiple myeloma (MM), peripheral neuropathy (PN) has for a long time been considered as mainly secondary to the plasma cell dyscrasia itself (particularly in POEMS syndrome), or following a direct compression (radicular or medullar), light chain deposits (amyloidosis), cryoglobulinemia or an autoimmune mechanism.[1-3] Treatment options are often limited by the fact that many of the most active agents in MM can cause or exacerbate an existing neuropathy and PN has been shown to negatively impact patients' quality of life.[4] Examples of these drugs causing treatment related neuropathy include vincristine, platinum containing agents (which are mostly of historic interest), and more recently, thalidomide and the proteasome inhibitor bortezomib. With the advent of these new drugs, the iatrogenic neurotoxicity has become the leading cause of PN. In addition, the therapeutic combinations associating these different drugs with or without conventional chemotherapy are currently being tested. Thus, the management of these new forms of PN has become important since it may limit the therapeutic prospects and may be a challenge for clinicians both in terms of diagnosis and treatment. We herein review and discuss the pathogenesis, incidence, risk factors, diagnosis, characteristics, and management of PN related to new MM drugs, mainly bortezomib and thalidomide.

For the purpose of this review, we performed an extensive search of the computerized database PubMed (MEDLINE), and the abstracts of meetings of the American Society of Hematology, European Hematology Association, American Society of Clinical Oncology, and EBMT (European Group for Blood and Marrow Transplantation) from 2000 to 2009. The keywords used for the search were: myeloma, neuropathy, chemotherapy-induced neuropathy, neurotoxicity, thalidomide, bortezomib, and Velcade®. Experts in the field of myeloma were also asked about ongoing or closed studies that had not yet been published.

Pathogenesis of peripheral neuropathy

The current knowledge of the pathophysiology of the new forms of PN is still limited.

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The mechanisms involved in general depend on the agents used, patient's medical history (e.g. history of diabetes), and duration of exposure and/or treatment doses.

Bortezomib

Although bortezomib-induced PN (BIPN) is usually easy to diagnose from a clinical point of view, its pathophysiology remains unclear. BIPN seems to be a proteasome-inhibitor class effect. In the rat, Cavaletti *et al.*[5] demonstrated that bortezomib induces a significant and dose-dependent reduction in the sensory nerve fibers' conduction velocities, with recovery taking several weeks. Sciatic nerve examination and morphometric determinations demonstrated mild to moderate pathological changes, involving predominantly the Schwann cells and myelin, although axonal degeneration was also observed. Bortezomib-induced changes were also observed in dorsal root ganglia (DRG) neurons and they were represented by satellite cell intracytoplasmatic vacuolization due to mitochondrial and endoplasmic reticulum damage, closely resembling the changes observed in sciatic nerve Schwann cells. In another study, it was also shown that the primary target for proteasome inhibitor-induced PN was the DRG neuronal cell bodies. After proteasome inhibition *in vivo*, chromatolysis of DRG neurons was observed, followed by cytoplasmic accumulation of eosinophilic material. Evidence of neurofilaments and juxtanuclear electron-dense cytoplasmic deposits was also noted within the DRG neurons. These lesions were likely related to blood and cellular proteasome inhibition levels.[6] At the molecular level, mitochondrial and endoplasmic reticulum damage seems to play a key role in BIPN, since bortezomib is able to activate the mitochondrial-based apoptotic pathway.[7] Co-treatment with a panel of Ca++ modulating agents identified the mitochondrial uniporter as a critical determinant in bortezomib cytotoxicity, suggesting that mitochondrial mediated dysregulation of Ca++ homeostasis is a critical regulator of bortezomib cytotoxicity.[8] Furthermore, there could potentially be a dysregulation of the neurotrophic factors since bortezomib inhibits the activation of NFκ-B, thereby blocking the transcription of the trophic Nerve Growth Factor.[5] In another work, Poruchynsky *et al*. demonstrated that proteasome inhibitors increase tubulin polymerization and stabilization in tissue culture cells. This microtubule stabilization represents a possible mechanism contributing to BIPN and cellular toxicity following proteasome inhibition with bortezomib.[9] Finally, it is also increasingly recognized that BIPN may be triggered by some autoimmune or inflammatory factors.[10,11]

Thalidomide

The mechanisms of thalidomide-induced PN (TIPN) are also not clear. Diverse mechanisms may be involved: reduction in nerve blood supply due to the anti-angiogenic properties of thalidomide, direct toxic effects of thalidomide on neurons of the posterior root ganglia or dysregulation of neurotrophin activity through effects of thalidomide on NFκ-B. In fact, alteration in the usual process of Wallerian degeneration due to a reduction in TNF-α, and secondary inhibition of NFκ-B has already been described. Studies based on sural nerve biopsies have shown signs of Wallerian degeneration and a selective loss of large diameter fibers without demyelinization.[12] More recently, Johnson *et al.* have shown that genetic variations in genes involved in drugs' neurotoxicity are likely to impact on whether an individual patient will develop this adverse effect. The most significant SNPs associated with TIPN were seen in the ADME genes group (drug Absorption, Distribution, Metabolism and Excretion), ABC, cytochromes and solute carrier families' genes. Significant associations were also seen in genes involved in neurological system processes and central nervous system development (*ERBB2, NQO1, MY03A, PPARD, DBH, NGFR, GSTP1, TCF8* and *ICF1R*).[13]

Clinical aspects

Bortezomib

The clinical profile of BIPN is quite characteristic. Although some rare cases of sudden polyradiculoneuritis may occur, BIPN typically occurs within the first treatment cycles with bortezomib, reaches a plateau around cycle 5, and does not appear to increase thereafter[10,14] (Table 1). It is more a sensory rather than a motor PN (pain, paresthesia, burning sensation, dysesthesia, numbness, sensory loss) affecting the feet more than the hands.[5] Patients may present a suppression/reduction in their deep tendon reflexes (DTR) in proportion to sensory loss and changes in proprioception and vibratory sensitivity.[15] Indeed, Cata *et al*. described a significantly elevated touch detection threshold and slotted peg board time, impaired sharpness detection, and elevated thresholds for the detection of skin warming and heat pain. Patients also had increased reports of cold pain, indicating that BIPN is associated with deficits in all fiber types in sensory nerves.[15] 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.[16] From the electrophysiological standpoint, nerve conduction study predominantly reveals low amplitude of sensory action potentials, in keeping with a length-dependant, sensory, axonal polyneuropathy, with predominant small-fiber involvement.[17]

Motor impairment is rare, even if the pain and stinging of the extremities result in a reduction in activity complicating the diagnosis of pure muscular weakness. However, grade 1 to 3 motor neuropathy, consisting of mild to severe distal weakness in the lower limbs, may occur in approximately 10% of patients with cases of life-threatening grade 4 motor neurotoxicity.[18,19]

In terms of dysautonomic neurotoxicity, orthostatic hypotension has been reported in about 10% of the patients. The pooled data from 228 patients treated in phase II trials[20,21] revealed orthostatic/postural hypotension in 27 (12%) patients (4% grade 3, no grade 4). This complication is often dose-dependant and can be difficult to recognize and manage.

Thalidomide

The neurological complications usually occur after prolonged exposure: 70% of the patients treated for 12 months will develop PN. The clinical manifestations include bilateral and symmetrical sensory disorders, rarely motor disor-

ders or dysautonomia. Patients can experience stinging sensations or numbness (distal paresthesia and hyperesthesia) that initially affect the toes, sometimes the fingers, and that may extend proximally. Trembling is very common but rarely interferes with daily activities in the initial stage. Later, the deep vibratory sensitivity and proprioception may be affected, leading to progressive ataxia, difficulty in walking and trembling when posture is maintained.

From the electrophysiological standpoint, thalidomide is most frequently reported to cause a length-dependent axonal neuropathy.[22] Symptoms are rather sensory and affect small and large diameter fibers. Motor impairment is rare but possible in the most severe cases. However, Mileshkin *et al*. found that motor nerve electrophysiological study (NES) changes were seen commonly and frequently developed concurrently with sensory changes,[23] suggesting that thalidomide frequently causes a sensorimotor axonal neuropathy, in contrast to bortezomib, which causes a predominantly sensory neuropathy. The cardinal sign on NES is a 50% decrease in the sensory nerve action potential (SNAP) amplitude, with relative conservation of nerve conduction velocities.[12]

Incidence, severity and risk factors of bortezomib-induced peripheral neuropathy

Incidence and severity of bortezomib-induced PN

BIPN was first reported in phase I trials.[24] This data has been confirmed in phase II trials (SUMMIT)[20] and CREST),[21] and in the pivotal phase III trial (APEX)[25] Richardson *et al*. assessed the frequency, characteristics and reversibility of PN occurring under bortezomib in the two SUMMIT/CREST trials.[14] The pooled analysis of both trials revealed that PN was observed in 35% of the patients including 37% of the patients treated with 1.3 mg/m^2 and 21% of those treated with 1 mg/m^2. The incidence of grade 1 or 2, 3 and 4 PN was 22%, 13% and 0.4%, respectively. A dose reduction was necessary in 12% of the patients and 5% of the patients had to discontinue treatment. Among patients who developed PN, a full resolution or an improvement of the PN was reported in most of the patients during follow-up (in 51% of the patients with grade ≥2 PN, and in 71% of the patients with grade 3, 4 PN or with PN resulting in treatment discontinuation). The median time to improvement or resolution of the PN was 47 (range, 1-529) days. Among patients without PN in the SUMMIT/CREST trials, 41 were included in the extension of the SUMMIT trial: only 5 (12%) of these patients presented PN after the additional courses of bortezomib. In spite of a prolonged treatment, most of the patients who had presented a PN in the SUMMIT/CREST trials did not report an aggravation of the PN, demonstrating that prolonged exposure to bortezomib does not increase the incidence or severity of the PN.[14]

In the large randomized phase III trial (APEX), 669 patients with relapsed or refractory MM were randomized to bortezomib or dexamethasone. Bortezomib was held, dose-reduced or discontinued depending on PN severity, according to a protocol-specified dose-modification guideline. The frequency, characteristics and reversibility of PN in this trial was recently assessed by Richardson *et al*.[26]

Table 1. Characteristics of bortezomib- and thalidomide-related peripheral neuropathy.

Thalidomide	Bortezomib
Very high incidence (>70% in certain trials) Grade 1-2 ~50% Grade 3-4 ~20%	Overall incidence < 40% Grade 1-2 ~30% Grade 3-4 <10%
Mainly sensory, but often motor signs	Mainly sensory, rarely motor signs Often painful neuropathy
Increased risk with prolonged administration	Not all patients will develop PN
Often limits the dose and the duration of treatment	May be managed with dose adjustment
Often irreversible	Reversible in >50% of patients, particularly if are adhered to the dose adjustment recommendations

Overall, 37% of patients assigned to the bortezomib arm had BIPN, including 27% with grade ≥2, 9% with grade ≥3, and <1% with grade 4. The cases of PN were mainly sensory. Motor PN was rare. Of patients with grade ≥2 PN, 64% experienced improvement or resolution to baseline at a median of 110 (range, 4–627) days, including 68% who had dose modification versus 47% who did not. Moreover, efficacy did not appear adversely affected by dose modification for grade ≥2 PN. Incidence and severity were not affected by age, number/type of prior therapies, baseline glycosylated hemoglobin level, or diabetes history. The authors concluded that the lower frequency of grade ≥3 PN in the APEX trial might be due to the use of established dose-modification guidelines and to increasing investigator awareness of neuropathy, which was not the case in the SUMMIT/CREST trials.[26,27]

More recently, in the VISTA trial,[28] testing bortezomib plus melphalan and prednisone for initial treatment of MM, sensory PN was reported more frequently in the bortezomib group, including grade 1 neuropathy in 14%, grade 2 in 17%, grade 3 in 13%, and grade 4 in <1% of patients. At time of data cut-off, 74% of PN events had either resolved (56%) or decreased by at least one toxicity grade (18%) within a median of two months, consistent with the rate reported in previous studies, taking into account the duration of therapy and the cumulative dose of bortezomib. In another recent single-center retrospective series of 100 patients treated with bortezomib, the incidence of PN was 38% with only 5 cases of grade 3 PN and one case of grade 4 PN. The median time to PN occurrence was 53 (range, 11-182) days. In the 38 patients who developed PN, a resolution or an improvement in the symptoms was noted in 53% of the cases in a median period of three months (range, 1-8). In multivariate analysis, the total number of bortezomib cycles (<4 or >4 cycles) and a past history of treatment with thalidomide were the significant predictive factors for the development of PN.[18]

Risk factors for bortezomib-induced peripheral neuropathy

When considering therapeutic combinations, several trials combined bortezomib with other drugs known for their neurotoxic properties. The concomitant use of other agents does not seem to affect the risk of PN, in particular the

addition of thalidomide. For instance, in the trials assessing bortezomib in combination with thalidomide, the incidence of grade 3-4 PN was relatively low.[29] This was rather surprising since the two drugs are known to be neurotoxic. Although this may be due to a selection bias, it is possible that thalidomide has a protective effect with respect to bortezomib through its anti-inflammatory action, that inhibits TNF-α.[29] However, in another study by Chaudhry *et al*. assessing 27 previously untreated MM patients, at the end of treatment with bortezomib and thalidomide, PN developed in 26 patients. PN was of mild to moderate severity (grade 1=11, grade 2=10, grade 3=5, and grade 4=0), suggesting that using those two neurotoxic agents together has limitations, even though 80% of patients had become asymptomatic after discontinuation of the chemotherapy.[10] More interestingly, it is worthy of note that some patients receiving a salvage treatment with lenalidomide presented a significant improvement in their PN symptoms which may be attributable primarily to the abbreviated doses of bortezomib that were used and/or the putative anti-inflammatory action of lenalidomide.[29] Therefore, further larger studies are needed to support the finding of symptomatic improvement of BIPN after IMID administration.

As a first-line treatment, the use of bortezomib with dexamethasone (± doxorubicine) did not induce grade 3 or 4 PN more often than in the relapsed patients.[30,31] The trials carried out with bortezomib in first line demonstrated a similar incidence of PN compared with the patients treated after a relapse. Harrousseau *et al*.[32] reported a cumulative incidence of PN of 30% (6% grade 3 and 4% discontinuation of treatment due to PN), while Jagannath *et al*.[30] observed a 31% rate including 16% grade 3. In both trials, no predisposing factors for this PN were detected. Interestingly, when bortezomib and dexamethasone were administered as a pre-transplant induction regimen on an alternating schedule in the recent Spanish phase II PETHEMA trial,[33] a very low PN rate was observed (22.5% grade 1, 2.5% grade 2 and no grade 3 or 4), which seems to be a promising schedule.

But one should keep in mind that the disease itself may represent an important contributing factor to BIPN genesis since a significant portion of chemotherapy-naive patients with newly diagnosed MM are found to have neuropathy symptoms at baseline (3-20% according to studies).[4,34,35]

Indeed, the impact of a pre-existing PN is still a matter of debate. About 80% of the patients included in phase II trials (SUMMIT/CREST) already presented PN at time of inclusion (with 48% already having some functional deficiency with sensory or motor symptoms). Seventy-five percent of the patients had received a prior treatment with vincristine, 72% with thalidomide and 36% with cisplatin. The incidence of grade 3 PN was higher in patients with pre-existing PN at time of inclusion, compared with those without PN (14% *vs.* 4%). Although more severe PN was found in cases of pre-existing PN before the treatment, the global incidence of PN was independent of the presence of an initial PN or the type of prior treatment received.[14] In the APEX trial, 67% of patients reported PN symptoms at baseline. The overall incidence of treatment-emergent PN in these patients was 39%, including 11% grade ≥3, compared with 38% and 5% in patients without baseline symptoms. In a retrospective study, Badros *et al*. evaluated the incidence, severity and risk factors of PN in a population of 78 relapsed or refractory MM patients treated with bortezomib alone or in combination.[29] Before treatment, 37% of the patients presented grade 1 or 2 PN. After treatment, 52% developed PN (including 15% and 7% grade 3 and 4, respectively). Although the retrospective design and the elevated number of patients with pre-existing neuropathy or diabetes mellitus (DM) may have biased the interpretation of results, this study showed that pre-existing PN was a significant predictive factor for the appearance or aggravation of PN. Similarly, in the VISTA trial, patients with baseline grade 1 PN (9%) had an increased risk of treatment-emergent/worsening PN. In fact, pre-existing neuropathy appeared to be the only consistent baseline risk factor in this trial.[28] The latter findings were further supported by data from Lanzani *et al.* showing that the course of BIPN is generally more severe in patients with the highest baseline PN.[36] Obviously, more studies are still needed before drawing definitive conclusions as to the role of a pre-existing PN to BIPN. However, it is likely that a pre-existing PN would represent a significant additional factor warranting careful assessment of the benefit/risk ratio if bortezomib is to be used.

When considering the impact of age, in the phase II trial by Mateos *et al*. testing VMP,[37] age seemed to play a major role since the incidence of PN was higher in patients over 75 years (25%) as compared to patients under 75 years (14%). But in the phase III VISTA trial,[28] there was no significant difference in the incidence and severity of BIPN according to age. Also, different studies could not show a significant impact of age *per se* as a risk factor for PN.[25,26,29] Finally, in the future, other drug combinations such as tanespimycin (which targets HSP90) with bortezomib may modify the natural history of BIPN.[38] One should also bear in mind that novel irreversible proteasome inhibitors, NPI-0052 and carfilzomib, are being developed and clinical trials are underway in myeloma and other solid tumors. Novel agents such as carfilzomib may have a different toxicity profile in terms of PN, while showing increased efficacy compared with bortezomib and being active against bortezomib-resistant myeloma cell lines and samples from patients with clinical bortezomib resistance.[39]

Incidence, severity and risk factors of thalidomide-induced peripheral neuropathy

Thalidomide was introduced in the treatment of MM about ten years ago. The first study was published by Singhal *et al*.[40] and since then thalidomide has proved to be a major treatment for replased or *de novo* MM. The incidence of TIPN varies greatly according to the different studies, since the criteria for the evaluation and rating differ (electro-physiological or clinical criteria), the follow-up is generally short, and the cohorts are not always comparable. The overall incidence of PN ranges from 25 to 83%, with about 15% of the patients having to interrupt their treatment.[23,41,42] In a meta-analysis of 42 phase II trials on thalidomide used as a single agent in 1,674 relapsed or refractory MM patients, Glasmacher *et al*.[43] reported an incidence of grade 3-4 PN of about 6%. Predictive factors for the appearance of PN with thalidomide are not yet clearly established, and the studies are sometimes even

contradictory. In the *Total Therapy 2* (TT2) study,[44] 668 newly diagnosed patients were treated with double autologous transplantations, with a randomization between 400 mg of thalidomide or not during induction, and between low dose of thalidomide or not during the consolidation-maintenance phase. In this trial, the incidence of PN was higher in patients aged over 65 years (41% *vs.* 17%, $P<0.001$). In other studies,[23,45,46] the relative risk of developing TIPN was not influenced by age, sex, type of prior treatment (including vincristine), or even abnormalities in the electrophysiological examinations at baseline.[23]

The relationship between PN, duration of exposure, dose-intensity and cumulative dose of thalidomide remains controversial. Several trials have demonstrated that PN was more likely to appear with a high cumulative dose and that it aggravates with the highest administered doses.[47-50] A few studies have suggested a lower risk of PN with low doses. In two successive trials, Rajkumar *et al*. reported PN in 50-80% of the patients, and this was correlated with the dose and duration of treatment.[51,52] Offidani *et al*.[45] found that the incidence of PN was dose-dependent, with a significant cut-off for the development of PN at 150 mg/day. In the meta-analysis by Glasmacher *et al*., the cut-off was at 200 mg/day.

However, other trials did not find a significant link between the cumulative dose and the occurrence of PN. Tosi *et al*.[46] reported the long-term toxicity results in 40 patients that had received thalidomide ± dexamethasone (with evaluations by NES in the most severe cases). The overall incidence of PN was 75%. In this trial, the risk of PN was mainly correlated with the duration of treatment, and not with the cumulative or daily dose of thalidomide. Another study by Mileshkin *et al*.[23] assessed the time course, predictive factors and utility of serial NES in the development of PN in 75 relapsed/refractory MM patients, that had been treated with increasing doses of thalidomide±IFN-α. Patients were clinically and electrophysiologicaly monitored (NES every three months). Thirty-nine percent of patients had NES abnormalities at baseline, yet no patients had a clinical neuropathy greater than grade 1 at enrollment. Forty-one percent developed PN (32% grade 2) during therapy and 15% had to discontinue the treatment due to toxicity. The actuarial incidence of PN rose dramatically between six and 12 months from 38% to almost 73%. The patients who developed PN in this trial received a median of 268 days of thalidomide, as compared with 89 days for those who did not develop PN ($P=0.0001$). Interestingly, the major predictor of developing PN was found to be the duration of exposure to thalidomide, rather than on the cumulative dose or dose-intensity. Based on these findings and review of the literature, including 12 studies addressing the relationship between cumulative dose and the development of PN, Mileshkin *et al*.[23] recommended no more than six months of thalidomide therapy with optimal dosing, with the possible exception of elderly patients who may require prolonged therapy. Other trials have corroborated these results since it appears that even with low doses, patients may still develop PN if they were exposed to thalidomide for a long time.[53-55] This latter issue is crucial since there is still controversy in the literature as to the efficacy of low doses of thalidomide.[56] In a prospective randomized trial testing a dose of 400 mg/day *vs.* 100 mg/day, Yakoub-Agha *et al*.[56] noted that the 100 mg/day dose was better tolerated with a significant reduction in drowsiness, constipation, and PN. In this perspective, one can speculate that it may be possible to maintain thalidomide treatment with a reduced dose without aggravating the PN. In summary, the above different studies suggest that age, duration of exposure, dose-intensity and cumulative doses may influence the incidence of TIPN to different degrees. Although the use of low doses may prove effective and better tolerated (particularly for drowsiness), the long-term neurological toxicity persists and should be taken into account.[12] More recently, the advent of new generation IMID (lenalidomide) seems promising since these thalidomide-analogs are less toxic in terms of PN, while having a greater immunomodulatory activity and a superior safety profile compared to thalidomide.

Indeed, in a phase II trial[57] testing lenalidomide (30 mg/day) in relapsed/refractory MM patients, the incidence of PN was 10%, with only 3% of grade 3. In another large study by Richardson *et al*.,[58] no cases of lenalidomide-related grade 3 or 4 PN were reported, with grade 2 PN reported in 6 (3%) patients. Finally, the incidence of severe PN barely exceeds 2% in the two major pivotal phase III trials,[59,60] comparing lenalidomide-dexamethasone versus dexamethasone alone.

Table 2. Guidelines for the management of bortezomib and thalidomide-induced PN evaluated according to the National Cancer Institute's Common Terminology Criteria for Adverse Events.

Bortezomib	Thalidomide
Grade 1 (paresthesia, weakness and/or loss of reflexes without pain or loss of function):	
▶ No action	▶ No action
Grade 1 with pain or Grade 2 (interfering with function but not with daily activities):	
▶ Reduce bortezomib to 1.0 mg/m^2	▶ Reduce thalidomide dose to 50% or suspend thalidomide until disappearance of toxicity, then re-initiate at 50% dose
Grade 2 with pain or Grade 3 (interfering with daily activities):	
▶ Suspend bortezomib until disappearance of toxicity then re-initiate at 0.7 mg/m^2 and administer once weekly	▶ Suspend thalidomide until disappearance of toxicity, then re-initiate at low dose if PN ≤grade 1
Grade 4 (permanent sensory loss interfering with function):	
▶ Discontinue bortezomib	▶ Discontinue thalidomide

Practical recommendations

Assessment of bortezomib-induced peripheral neuropathy

A regular clinical evaluation of the symptoms and performance status, before the beginning and during treatment are essential to monitor clinical changes. Early diagnosis may be essential, especially as there is a small subgroup of patients who develop severe PN soon after starting bortezomib. Therefore, there is an urgent need for developing a clinically easy to use and effective diagnosis and staging system. In the APEX study, 45% of patients who discontinued due to grade ≥2 PN did so within the first three cycles.

Although authors usually focus on the severe grade 3-4 PN, special attention should be drawn to grade 2 PN with pain since such manifestations can significantly impact patients' quality of life. Patients should be encouraged to immediately report the slightest functional difficulty or restriction (writing, getting dressed, doing and undoing buttons, etc.). However, such a type of assessment may introduce a certain subjectivity from the patients, and limits the comparability of the trials.[61] Accurate grading of BIPN is still controversial. Several questionnaires or scales can be used.[62-65] Recently, the Total Neuropathy Score,[66] a composite measure that includes symptoms, signs, ability aspects, and electrophysiological measures, has been shown to be valid in patients having chemotherapy induced PN (CIPN). However, none of the currently available scales is a firmly established measure in BIPN, and their validity and reliability should be tested in future studies assessing neurotoxicity in patients treated with bortezomib. In our opinion, the optimal grading scale for assessing neurotoxicity would probably include the use of a combination with grading scale of pain intensity and electrophysiological measures.

Outcome of bortezomib-induced peripheral neuropathy

Since BIPN is dose-dependent and often reversible, the use of an algorithm of modifications for the treatment regimen is required. BIPN can improve, stabilize or completely resolve in most patients upon discontinuation or reduction of bortezomib doses after a median interval of three months.[14] However, one should bear in mind that the median duration of improvement is longer with grade 3-4 impairments than with grade 1-2 impairments. Dose reduction algorithm, longer intervals between cycles, but also a weekly instead of a twice-weekly administration schedule, are effective strategies to prevent aggravation of symptoms. The occurrence of PN with pain requires a dose reduction under the classical dose of 1.3 mg/m^2. Interestingly, in the CREST trial, the incidence of BIPN was lower with the 1 mg/m^2 dose, suggesting that it is possible to continue the treatment with a low dose in patients who do not well tolerate the 1.3 mg/m^2 dose while maintaining good therapeutic efficacy. Moreover, a recent study comparing two regimen bortezomib-melphalan-prednisone (VMP) *versus* bortezomib-melphalan-prednisone-thalidomide (VMPT) in up-front therapy for patients older than 65 years, Palumbo *et al*. showed that weekly infusion of bortezomib significantly reduced the incidence of grade 3–4 PN (18% in the biweekly *vs.* 9% in the weekly schedule for the VMPT arm, and 12% in the biweekly *vs.* 3% in the weekly schedule for the VMP arm) without influencing outcome.[67] The beneficial impact of a weekly administration schedule of bortezomib in terms of BIPN could be also shown in the Spanish multicenter study by Mateos *et al*. comparing VMP *versus* VTP (bortezomib-thalidomide-prednisone).[68]

Treatment of bortezomib-induced peripheral neuropathy

The treatment of BIPN is usually symptomatic. Treatment with analgesics or anti-depressants may be beneficial (such as amitriptylline, serotonin uptake inhibitors, duloxetine or antiepileptic agents, such as gabapentine). The use of topical skin agents may be useful in certain patients (capsaicin cream). Certain authors have used low doses of vitamin supplements (B6, C, L-carnitine). However, one should be cautious since high doses of pyridoxine may induce lesions of the sensory neurons (especially in case of renal insufficiency or low-protein diet).[69,70] The use of high doses of vitamin C is also not recommended since it may interfere with the metabolism of bortezomib and reduce its efficacy.[71,72] More recently, Colvin *et al*. described a case of a rapid reversal of BIPN by using the topical transient receptor potential melastatin (*TRPM8*) receptor activator, menthol.[73] Based on our experience, in case of BIPN, we propose first to use pregabalin 150-600 mg/day for at least three months. Gabapentin (300-2,400 mg/day) is another alternative and the highest tolerated doses should be aimed. In case of failure, duloxetine (30-60 mg/day) is a valid second-line choice. We also suggest the use of tramadol to fight against chronic pain.[74] In addition to pharmacological measures, we also advise the patient to: (i) wear loose-fitting shoes, roomy cotton socks, and padded slippers; (ii) keep feet uncovered in bed since bedding that presses down on the toes can add to the problem; (iii) walk to help blood circulate in the feet, though too much walking or standing can make the problem worse; and (iv) soak feet in icy water (or the coldest water available) and massage the feet for temporary pain relief.

When considering dysautonomic side-effects, especially if myeloma is complicated by Al amyloidosis, bortezomib should be used cautiously in patients with a history of syncope, receiving medications known to be associated with hypotension or who are dehydrated. Management of orthostatic/postural hypotension may include adjustment of antihypertensive medications, hydration, increased salt intake, or the administration of corticosteroids with mineralocorticoid effects. Patients should rise slowly, keep physically active, and drive vehicles or operate machinery with caution. They should report any episodes of hypotension or symptoms of light-headedness, dizziness, or fainting. This symptom may be reduced by concomitant hydration (500 mL normal saline) with each dose of bortezomib.[75]

In all, it is likely that with: (i) a systematic neurological examination at the beginning of bortezomib treatment (particularly in those patients who received prior neurotoxic agents such as vincristine, cisplatine or thalidomide); (ii) compliance with the rules of treatment schedule modifications for patients presenting *de novo* PN or aggravation of a pre-existing PN; and (iii) a switch towards a weekly administration schedule (especially in case of combinations such as bortezomib, thalidomide and dexamethasone), the incidence and management of BIPN will be less problematic (Table 2).

Thalidomide-induced peripheral neuropathy

In addition to patients' awareness, regular clinical monitoring is mandatory. Although some authors recommended systematic NES tests, their usefulness has never really been demonstrated. The results of the study by Mileshkin *et al*. that assessed patients by means of neurophysiological examinations every three months, demonstrated that close clinical monitoring is as effective as regular electrophysiological assessments. NES did not reliably predict the onset of significant PN and frequently did not correlate with clinical findings.[23] The lack of correlation between NES results

and the clinical features of TIPN was also reported in non-myeloma patients.[76]

Before the sensory PN becomes painful, complicated by motor deficiency or interferes with daily activities, it is necessary to reduce or discontinue thalidomide.[77] In contrast to BIPN, if thalidomide is not interrupted quickly, PN symptoms can often aggravate and become irreversible. Since the occurrence of TIPN is not predictable and a preventive treatment still does not exist, it is important to minimize other potential risk factors for PN such as vitamin B12 deficiency. Indeed, a recent study demonstrated that Vitamin B12 deficiency occurred in 13.6% of patients with plasma cell dyscrasia.[78] Moreover, diabetes must always be considered since it predisposes to PN and thalidomide has been involved in the aggravation of the glycemic balance.[79] The symptomatic treatment of this PN does not differ from that of BIPN.

Concluding remarks

New treatments with bortezomib or thalidomide have improved the outcome of patients with MM. Therefore, the management of PN is becoming a major challenge and further studies are still required to accurately assess PN risk factors. The elucidation of neurotoxicity pathogenesis will hopefully help facilitate the identification of more effective and safe neuroprotective strategies. Electrophysiological assessments may support the diagnosis, although their contribution remains insufficient since most of the symptoms for both drugs derive primarily from the damage of the small nerve fibers that are not well investigated by routine electrophysiological techniques. A full anamnesis and regular clinical evaluation are necessary. Complex clinical features may require a specialized neurological evaluation within the context of a multi-disciplinary approach. However, there is a need for a simple, widely usable, and effective grading system. Early detection of PN and the use of dose adjustment algorithms or modification of administration schedules, as in the case of bortezomib, should help reduce the side effects while maintaining anti-tumor efficacy.

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BM: performed bibliographic search, wrote and revised the manuscript; JE-C: performed bibliographic search and commented on the manuscript; IY-A: performed bibliographic search and commented on the manuscript; PM: performed bibliographic search and commented on the manuscript; J-LH: performed bibliographic search and commented on the manuscript; MM: performed bibliographic search, wrote and revised the manuscript.

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References

1. Dispenzieri A, Kyle RA. Neurological aspects of multiple myeloma and related disorders. Best Pract Res Clin Haematol. 2005;18(4):673-88.
2. Denier C, Lozeron P, Adams D, Decaudin D, Isnard-Grivaux F, Lacroix C, et al. Multifocal neuropathy due to plasma cell infiltration of peripheral nerves in multiple myeloma. Neurology. 2006;66(6):917-8.
3. Drappatz J, Batchelor T. Neurologic complications of plasma cell disorders. Clin Lymphoma. 2004;5(3):163-71.
4. Silberman J, Lonial S. Review of peripheral neuropathy in plasma cell disorders. Hematol Oncol. 2008;26(2):55-65.
5. Cavaletti G, Gilardini A, Canta A, Rigamonti L, Rodriguez-Menendez V, Ceresa C, et al. Bortezomib-induced peripheral neurotoxicity: a neurophysiological and pathological study in the rat. Exp Neurol. 2007;204(1):317-25.
6. Silverman L CL, Kadambi VJ, Decoster R, Vynckier A, Jortner B, Alden CL. Model for proteasome inhibition associated peripheral neuropathy. Toxicologic Pathology [Abstract]. 2006;34(989).
7. Pei XY, Dai Y, Grant S. Synergistic induction of oxidative injury and apoptosis in human multiple myeloma cells by the proteasome inhibitor bortezomib and histone deacetylase inhibitors. Clin Cancer Res. 2004;10(11):3839-52.
8. Landowski TH, Megli CJ, Nullmeyer KD, Lynch RM, Dorr RT. Mitochondrial-mediated disregulation of Ca2+ is a critical determinant of Velcade (PS-341/bortezomib) cytotoxicity in myeloma cell lines. Cancer research. 2005;65(9):3828-36.
9. Poruchynsky MS, Sackett DL, Robey RW, Ward Y, Annunziata C, Fojo T. Proteasome inhibitors increase tubulin polymerization and stabilization in tissue culture cells: a possible mechanism contributing to peripheral neuropathy and cellular toxicity following proteasome inhibition. Cell cycle (Georgetown, Tex. 2008 Apr 1;7(7):940-9.
10. Chaudhry V, Cornblath DR, Polydefkis M, Ferguson A, Borrello I. Characteristics of bortezomib- and thalidomide-induced peripheral neuropathy. J Peripher Nerv Syst. 2008;13(4):275-82.
11. Ravaglia S, Corso A, Piccolo G, Lozza A, Alfonsi E, Mangiacavalli S, et al. Immune-mediated neuropathies in myeloma patients treated with bortezomib. Clin Neurophysiol. 2008;119(11):2507-12.
12. Mileshkin L, Prince HM. The troublesome toxicity of peripheral neuropathy with thalidomide. Leuk Lymphoma. 2006; 47(11):2276-9.
13. Johnson DC. Genetic Variation in ADME Genes Is Associated with Thalidomide Related Peripheral Neuropathy in Multiple Myeloma Patients. Blood ASH Annual Meeting Abstract. 2008 Nov 2008;112(11): 1675.
14. Richardson PG, Briemberg H, Jagannath S, Wen PY, Barlogie B, Berenson J, et al. Frequency, characteristics, and reversibility of peripheral neuropathy during treatment of advanced multiple myeloma with bortezomib. J Clin Oncol. 2006;24(19):3113-20.
15. Cata JP, Weng HR, Burton AW, Villareal H, Giralt S, Dougherty PM. Quantitative sensory findings in patients with bortezomib-induced pain. J Pain. 2007;8(4):296-306.
16. Argyriou AA, Iconomou G, Kalofonos HP. Bortezomib-induced peripheral neuropathy in multiple myeloma: a comprehensive review of the literature. Blood. 2008;112(5): 1593-9.
17. Meisler AI. Bortezomib in multiple myeloma. N Engl J Med. 2003;349(13):1287-8; author reply.
18. El-Cheikh J, Stoppa AM, Bouabdallah R, de Lavallade H, Coso D, de Collela JM, et al. Features and risk factors of peripheral neuropathy during treatment with bortezomib for advanced multiple myeloma. Clinical lymphoma & myeloma. 2008;8(3):146-52.
19. Gupta S, Pagliuca A, Devereux S, Mufti GJ, Schey S. Life-threatening motor neurotoxicity in association with bortezomib. Haematologica. 2006;91(7):1001.
20. Richardson PG, Barlogie B, Berenson J, Singhal S, Jagannath S, Irwin D, et al. A phase 2 study of bortezomib in relapsed, refractory myeloma. N Engl J Med. 2003; 348(26):2609-17.
21. Jagannath S, Barlogie B, Berenson J, Siegel D, Irwin D, Richardson PG, et al. A phase 2 study of two doses of bortezomib in

relapsed or refractory myeloma. Br J Haematol. 2004;127(2):165-72.
22. Giannini F, Volpi N, Rossi S, Passero S, Fimiani M, Cerase A. Thalidomide-induced neuropathy: a ganglionopathy? Neurology. 2003;60(5):877-8.
23. Mileshkin L, Stark R, Day B, Seymour JF, Zeldis JB, Prince HM. Development of neuropathy in patients with myeloma treated with thalidomide: patterns of occurrence and the role of electrophysiologic monitoring. J Clin Oncol. 2006;24(27):4507-14.
24. Orlowski RZ, Stinchcombe TE, Mitchell BS, Shea TC, Baldwin AS, Stahl S, et al. Phase I trial of the proteasome inhibitor PS-341 in patients with refractory hematologic malignancies. J Clin Oncol. 2002;20(22): 4420-7.
25. Richardson PG, Sonneveld P, Schuster MW, Irwin D, Stadtmauer EA, Facon T, et al. Bortezomib or high-dose dexamethasone for relapsed multiple myeloma. N Engl J Med. 2005;352(24):2487-98.
26. Richardson PG, Sonneveld P, Schuster MW, Stadtmauer EA, Facon T, Harousseau JL, et al. Reversibility of symptomatic peripheral neuropathy with bortezomib in the phase III APEX trial in relapsed multiple myeloma: impact of a dose-modification guideline. Br J Haematol. 2009;144(6):895-903.
27. San-Miguel JF. Frequency, characteristics, and reversibility of peripheral neuropathy (PN) in the APEX trial. Blood ASH Annual Meeting. 2005;106(11).
28. San Miguel JF, Schlag R, Khuageva NK, Dimopoulos MA, Shpilberg O, Kropff M, et al. Bortezomib plus melphalan and prednisone for initial treatment of multiple myeloma. N Engl J Med. 2008;359(9):906-17.
29. Badros A, Goloubeva O, Dalal JS, Can I, Thompson J, Rapoport AP, et al. Neurotoxicity of bortezomib therapy in multiple myeloma: a single-center experience and review of the literature. Cancer. 2007;110(5):1042-9.
30. Jagannath S, Durie BG, Wolf J, Camacho E, Irwin D, Lutzky J, et al. Bortezomib therapy alone and in combination with dexamethasone for previously untreated symptomatic multiple myeloma. Br J Haematol. 2005;129(6):776-83.
31. Oakervee HE, Popat R, Curry N, Smith P, Morris C, Drake M, et al. PAD combination therapy (PS-341/bortezomib, doxorubicin and dexamethasone) for previously untreated patients with multiple myeloma. Br J Haematol. 2005;129(6):755-62.
32. Harousseau JL, Attal M, Leleu X, Troncy J, Pegourie B, Stoppa AM, et al. Bortezomib plus dexamethasone as induction treatment prior to autologous stem cell transplantation in patients with newly diagnosed multiple myeloma: results of an IFM phase II study. Haematologica. 2006;91(11):1498-505.
33. Rosinol L, Oriol A, Mateos MV, Sureda A, Garcia-Sanchez P, Gutierrez N, et al. Phase II PETHEMA trial of alternating bortezomib and dexamethasone as induction regimen before autologous stem-cell transplantation in younger patients with multiple myeloma: efficacy and clinical implications of tumor response kinetics. J Clin Oncol. 2007;25(28):4452-8.
34. Borrello I. Bortezomib and Thalidomide Treatment of Newly Diagnosed Patients with Multiple Myeloma - Efficacy and Neurotoxicity. ASH Annual Meeting Blood. 2006;108(11):3579.
35. Richardson PG. A Multicenter Phase II Trial of Bortezomib in Patients with Previously Untreated Multiple Myeloma: Efficacy with Manageable Toxicity in Patients with Unexpectedly High Rates of Baseline Peripheral Neuropathy. Blood ASH Annual Meeting. 2005;106(11):2548.
36. Lanzani F, Mattavelli L, Frigeni B, Rossini F, Cammarota S, Petro D, et al. Role of a pre-existing neuropathy on the course of bortezomib-induced peripheral neurotoxicity. J Peripher Nerv Syst. 2008;13(4):267-74.
37. Mateos MV, Hernandez JM, Hernandez MT, Gutierrez NC, Palomera L, Fuertes M, et al. Bortezomib plus melphalan and prednisone in elderly untreated patients with multiple myeloma: results of a multicenter phase 1/2 study. Blood. 2006;108(7):2165-72.
38. Erlichman C. Tanespimycin: the opportunities and challenges of targeting heat shock protein 90. Expert opinion on investigational drugs. 2009;18(6):861-8.
39. Kuhn DJ, Chen Q, Voorhees PM, Strader JS, Shenk KD, Sun CM, et al. Potent activity of carfilzomib, a novel, irreversible inhibitor of the ubiquitin-proteasome pathway, against preclinical models of multiple myeloma. Blood. 2007;110(9):3281-90.
40. Singhal S, Mehta J, Desikan R, Ayers D, Roberson P, Eddlemon P, et al. Antitumor activity of thalidomide in refractory multiple myeloma. N Engl J Med. 1999;341(21): 1565-71.
41. Prince HM, Schenkel B, Mileshkin L. An analysis of clinical trials assessing the efficacy and safety of single-agent thalidomide in patients with relapsed or refractory multiple myeloma. Leuk Lymphoma. 2007; 48(1):46-55.
42. Plasmati R, Pastorelli F, Cavo M, Petracci E, Zamagni E, Tosi P, et al. Neuropathy in multiple myeloma treated with thalidomide: a prospective study. Neurology. 2007;69(6):573-81.
43. Glasmacher A, Hahn C, Hoffmann F, Naumann R, Goldschmidt H, von Lilienfeld-Toal M, et al. A systematic review of phase-II trials of thalidomide monotherapy in patients with relapsed or refractory multiple myeloma. Br J Haematol. 2006;132(5):584-93.
44. Barlogie B, Tricot G, Anaissie E, Shaughnessy J, Rasmussen E, van Rhee F, et al. Thalidomide and hematopoietic-cell transplantation for multiple myeloma. N Engl J Med. 2006;354(10):1021-30.
45. Offidani M, Corvatta L, Marconi M, Malerba L, Mele A, Olivieri A, et al. Common and rare side-effects of low-dose thalidomide in multiple myeloma: focus on the dose-minimizing peripheral neuropathy. Eur J Haematol. 2004;72(6):403-9.
46. Tosi P, Zamagni E, Cellini C, Plasmati R, Cangini D, Tacchetti P, et al. Neurological toxicity of long-term (>1 yr) thalidomide therapy in patients with multiple myeloma. Eur J Haematol. 2005;74(3):212-6.
47. Chaudhry V, Cornblath DR, Corse A, Freimer M, Simmons-O'Brien E, Vogelsang G. Thalidomide-induced neuropathy. Neurology. 2002;59(12):1872-5.
48. Fullerton PM, O'Sullivan DJ. Thalidomide neuropathy: a clinical electrophysiological, and histological follow-up study. Journal of neurology, neurosurgery, and psychiatry. 1968;31(6):543-51.
49. Molloy FM, Floeter MK, Syed NA, Sandbrink F, Culcea E, Steinberg SM, et al. Thalidomide neuropathy in patients treated for metastatic prostate cancer. Muscle & Nerve. 2001;24(8):1050-7.
50. Cavaletti G, Beronio A, Reni L, Ghiglione E, Schenone A, Briani C, et al. Thalidomide sensory neurotoxicity: a clinical and neurophysiologic study. Neurology. 2004;62(12): 2291-3.
51. Rajkumar SV, Dispenzieri A, Fonseca R, Lacy MQ, Geyer S, Lust JA, et al. Thalidomide for previously untreated indolent or smoldering multiple myeloma. Leukemia. 2001;15(8):1274-6.
52. Rajkumar SV, Hayman S, Gertz MA, Dispenzieri A, Lacy MQ, Greipp PR, et al. Combination therapy with thalidomide plus dexamethasone for newly diagnosed myeloma. J Clin Oncol. 2002;20(21):4319-23.
53. Wechalekar AD, Chen CI, Sutton D, Reece D, Voralia M, Stewart AK. Intermediate dose thalidomide (200 mg daily) has comparable efficacy and less toxicity than higher doses in relapsed multiple myeloma. Leuk Lymphoma. 2003;44(7):1147-9.
54. Durie BG. Low-dose thalidomide in myeloma: efficacy and biologic significance. Seminars in oncology. 2002;29(6 Suppl 17):34-8.
55. Kees M, Dimou G, Sillaber C, Drach J, Ackermann J, Lechner K, et al. Low dose thalidomide in patients with relapsed or refractory multiple myeloma. Leuk Lymphoma. 2003;44(11):1943-6.
56. Yakoub Agha I. A multicenter prospective randomized study testing non-inferiority of thalidomide 100 mg/day as compared with 400 mg/day in patients with refractory/relapsed multiple myeloma: Results of the final analysis of the IFM 01–02 study. ASCO meeting. 2006;7520.
57. Richardson PG, Blood E, Mitsiades CS, Jagannath S, Zeldenrust SR, Alsina M, et al. A randomized phase 2 study of lenalidomide therapy for patients with relapsed or relapsed and refractory multiple myeloma. Blood. 2006;108(10):3458-64.
58. Richardson P, Jagannath S, Hussein M, Berenson J, Singhal S, Irwin D, et al. Safety and efficacy of single-agent lenalidomide in patients with relapsed and refractory multiple myeloma. Blood. 2009 May 26. [Epub ahead of print]
59. Dimopoulos M, Spencer A, Attal M, Prince HM, Harousseau JL, Dmoszynska A, et al. Lenalidomide plus dexamethasone for relapsed or refractory multiple myeloma. N Engl J Med. 2007;357(21):2123-32.
60. Weber DM, Chen C, Niesvizky R, Wang M, Belch A, Stadtmauer EA, et al. Lenalidomide plus dexamethasone for relapsed multiple myeloma in North America. N Engl J Med. 2007;357(21):2133-42.
61. Postma TJ, Heimans JJ, Muller MJ, Ossenkoppele GJ, Vermorken JB, Aaronson NK. Pitfalls in grading severity of chemotherapy-induced peripheral neuropathy. Ann Oncol. 1998;9(7):739-44.
62. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. American journal of clinical oncology. 1982;5(6):649-55.
63. National Cancer Institute. Common Toxicity Criteria vesion 3.0. Available from http://ctepcancergov/forms/CTCv30.
64. Ajani JA, Welch SR, Raber MN, Fields WS, Krakoff IH. Comprehensive criteria for assessing therapy-induced toxicity. Cancer investigation. 1990;8(2):147-59.
65. Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. Cancer. 1981;47(1):207-14.

66. Cavaletti G, Bogliun G, Marzorati L, Zincone A, Piatti M, Colombo N, et al. Grading of chemotherapy-induced peripheral neurotoxicity using the Total Neuropathy Scale. Neurology. 2003;61(9): 1297-300.
67. Palumbo A. A Prospective, Randomized, Phase III Study of Bortezomib, Melphalan, Prednisone and Thalidomide (VMPT) Versus Bortezomib, Melphalan and Prednisone (VMP) in Elderly Newly Diagnosed Myeloma Patients. Blood ASH Annual Meeting. 2008;112(11):652.
68. Mateos MV. Bortezomib (Velcade)-Melphalan-Prednisone (VMP) Versus Velcade- Thalidomide-Prednisone (VTP) in Elderly Untreated Multiple Myeloma Patients: Which Is the Best Partner for Velcade: An Alkylating or An Immunomodulator Agent? Blood ASH Annual Meeting Blood. 2008;112(11).
69. Levine S, Saltzman A. Pyridoxine (vitamin B6) toxicity: enhancement by uremia in rats. Food Chem Toxicol. 2002;40(10):1449-51.
70. Levine S, Saltzman A. Pyridoxine (vitamin B6) neurotoxicity: enhancement by protein-deficient diet. J Appl Toxicol. 2004; 24(6):497-500.
71. Catley L, Anderson KC. Velcade and vitamin C: too much of a good thing? Clin Cancer Res. 2006;12(1):3-4.
72. Zou W, Yue P, Lin N, He M, Zhou Z, Lonial S, et al. Vitamin C inactivates the proteasome inhibitor PS-341 in human cancer cells. Clin Cancer Res. 2006;12(1):273-80.
73. Colvin LA, Johnson PR, Mitchell R, Fleetwood-Walker SM, Fallon M. From bench to bedside: a case of rapid reversal of bortezomib-induced neuropathic pain by the TRPM8 activator, Menthol. J Clin Oncol. 2008;26(27):4519-20.
74. Sindrup SH, Andersen G, Madsen C, Smith T, Brosen K, Jensen TS. Tramadol relieves pain and allodynia in polyneuropathy: a randomised, double-blind, controlled trial. Pain. 1999;83(1):85-90.
75. San Miguel J, Blade J, Boccadoro M, Cavenagh J, Glasmacher A, Jagannath S, et al. A practical update on the use of bortezomib in the management of multiple myeloma. Oncologist. 2006;11(1):51-61.
76. Hess CW, Hunziker T, Kupfer A, Ludin HP. Thalidomide-induced peripheral neuropathy. A prospective clinical, neurophysiological and pharmacogenetic evaluation. Journal of neurology. 1986;233(2):83-9.
77. Palumbo A, Facon T, Sonneveld P, Blade J, Offidani M, Gay F, et al. Thalidomide for treatment of multiple myeloma: 10 years later. Blood. 2008;111(8):3968-77.
78. Baz R, Alemany C, Green R, Hussein MA. Prevalence of vitamin B12 deficiency in patients with plasma cell dyscrasias: a retrospective review. Cancer. 2004;101(4):790-5.
79. Pathak RD, Jayaraj K, Blonde L. Thalidomide-associated hyperglycemia and diabetes: case report and review of literature. Diabetes care. 2003 ;26(4):1322-3.