Netherlands
The Journal of Medicine

ORIGINAL ARTICLE

Bortezomib-induced polyneuropathy

A.J.J. Rampen[1,4*], J.L.M. Jongen[2], I. van Heuvel[4], M. Scheltens-de Boer[2], P. Sonneveld[3], M.J. van den Bent[4]

[1]Department of Neurology, HagaZiekenhuis, The Hague, the Netherlands, Department of [2]Neurology and [3]Haematology, ErasmusMC, Rotterdam, the Netherlands, [4]Department of Neurology/Neuro-Oncology, ErasmusMC – Daniel den Hoed Oncologisch Centrum, Rotterdam, the Netherlands, [*]corresponding author: tel.: +31 (0)10-7041415, fax: + 31 (0)10-7041031, e-mail: ajjrampen@hotmail.com

ABSTRACT

Background: Peripheral neuropathy is a frequent side effect of bortezomib chemotherapy. Relatively little is known about the clinical characteristics of this neuropathy, especially with respect to pain. Our aim was to describe the clinical characteristics and course of bortezomib-induced polyneuropathy.

Methods: This is a retrospective cohort study of 39 patients diagnosed with bortezomib-induced polyneuropathy.

Results: Pain is the most prominent symptom and 14 of 39 patients suffered from severe pain. More than 50% of our patients used analgesics due to moderate or severe pain. We found no correlation between severity of symptoms of bortezomib-induced polyneuropathy and cumulative dose or dose intensity of bortezomib. Nerve conduction studies did not correlate well with symptom severity. Dose reduction or discontinuation of treatment reduced severity in most cases.

Conclusion: Painful polyneuropathy is a frequent, dose-limiting side effect of bortezomib with a relatively good prognosis. Careful neurological monitoring of symptoms and timely dose adjustment is important.

KEYWORDS

Bortezomib, multiple myeloma, neuropathy, pain

INTRODUCTION

Bortezomib (Velcade®) is a proteasome inhibitor and registered for the treatment of multiple myeloma, a relatively frequent haematological malignancy.[1] Ongoing trials are evaluating the efficacy in other haematological malignancies and solid tumours.[2] Proteasomes are protein complexes involved in protein degradation, including pro-apoptotic proteins which induce programmed cell death in (cancer) cells. Through complex molecular cascades proteasome inhibition leads to apoptosis of cancer cells.[3]

In phase I studies polyneuropathy was already identified as a side effect of bortezomib.[4] In subsequent phase II and III investigations, the reported incidence of bortezomib-induced polyneuropathy ranged between 30% and 64%.[1,5-9] The exact causative pathway of this polyneuropathy is not yet fully understood, but seems most likely to be multifactorial, to which genetic factors of both the patient and tumour contribute.[10]

Bortezomib-induced polyneuropathy has a typical glove-stocking distribution and, similar to polyneuropathies induced by thalidomide and vincristine, besides sensory symptoms also autonomous and mild motor symptoms can develop. However, unlike other chemotherapy-induced polyneuropathies, bortezomib-induced polyneuropathy can be remarkably painful. Patients can experience different modalities of neuropathic pain (for example, a burning sensation or very painful paraesthesia), which can greatly effect quality of life.

Little is known about the course of these symptoms (specifically pain) over time and their optimal treatment.

In this retrospective study we describe a group of patients with polyneuropathy due to bortezomib, who were followed over time.

MATERIALS AND METHODS

All patients referred to the outpatient clinic Neuro-Oncology/Neurology of the ErasmusMC between 2004 and 2008 with a polyneuropathy induced or aggravated by the use of bortezomib were included.

For these patients the following information was collected from their medical records:

1. Presence of a pre-existent polyneuropathy due to, for example, diabetes mellitus or previous use of neurotoxic chemotherapeutics, especially vincristine and thalidomide.
2. Bortezomib dosage regimen and the number of doses administered, combined with reasons for any dose reduction or premature cessation of the treatment. With these data we calculated the cumulative dose and dose intensity of bortezomib per patient.
3. Symptoms and signs of polyneuropathy and any treatment for neuropathic pain. For estimating the severity of polyneuropathy we used a score list which was specifically developed for assessing chemotherapy-induced polyneuropathy.[11,12] In this score symptoms experienced by the patient are combined with abnormalities in the neurological exam (see appendix). Maximum pain intensity was recorded using a numerical rating score (NRS).[13] An NRS pain intensity of 0 means no pain, an NRS pain intensity of 10 maximum pain. In addition, the severity of motor neuropathy, sensory neuropathy and neuropathic pain was scored separately using the Common Toxicity Criteria (CTC).[14] Finally, the effect of pain medication was investigated; a reduction of at least 30% in the NRS pain intensity, which is a generally accepted outcome measure in pain studies, was considered a favourable response.[15]
4. Nerve conduction studies (NCS). The NCS consisted of sensory nerve conduction of the median, ulnar and sural nerve and motor nerve conduction of the ulnar and peroneal nerve. Using age-adjusted local reference values a distinction between normal and abnormal nerves was made.[16] Depending on the abnormalities found, we considered patients to have a normal NCS, a sensory polyneuropathy or a mixed (sensory and motor) polyneuropathy.

Mean and standard error of the mean of normally distributed continuous variables and median and range of not normally distributed continuous and categorical variables were calculated.

RESULTS

Forty-three patients presented to the Neuro-Oncology/Neurology outpatient clinic before or during use of bortezomib for the treatment of multiple myeloma. Four patients were excluded from further analysis: one patient had a severe polyneuropathy after use of thalidomide that did not worsen during use of bortezomib and for three patients insufficient data were available regarding the timing and dosage of bortezomib and other potentially neurotoxic chemotherapeutics.

Table 1. *Demographic data and medical history*

	Mean ± SEM
Age	57.6 ± 1.29
	Number of patients
Gender (n=39)	
Male	29
Female	10
Medical history (n=39)	
Diabetes mellitus	2
Previous chemotherapy (n=39)	
None	17
Vincristine	8
Thalidomide	6
Vincristine and thalidomide	8

SEM = standard error of the mean.

In *table 1* the demographic data and medical history are described. In accordance with the prevalence of multiple myeloma our study population contained more men than women. A minority of the patients had diabetes mellitus, a considerable group of patients had been treated previously with vincristine and/or thalidomide.

In 23 patients pain was the presenting symptom. In some this pain was more specifically described as painful paraesthesias (n=6), burning (n=4) and cold (n=4). Other presenting symptoms were paraesthesias (n=11), numbness (n=3) and cold sensation (n=1). In our cohort no patients presented with motor symptoms.

Median NRS pain intensity of our 39 patients at the time of maximum symptoms was 6. Twenty-seven patients had NRS pain intensity of 5 or higher (i.e. moderate pain) and in 14 patients this was even 8 or higher (i.e. severe pain).

Table 2 shows the average cumulative dose and dose intensity, the median time to development of bortezomib-induced polyneuropathy, the median time to maximum (pain) symptoms of polyneuropathy, median sum of

Table 2. *Clinical data at time of maximum symptoms*

	Mean ± SEM
Cumulative dose (n=39)	18.37 ± 1.44 mg
Dose intensity (n=39)	0.189 ± 0.0073 mg/day
	Median (range)
Number of days to first symptoms of polyneuropathy (n=39)	67 (4-288)
Number of days to maximum symptoms of polyneuropathy (n=39)	130 (28-349)
NRS pain intensity (n=39)	6 (0-10)
Score list (n=38)	6 (1-11)
CTC	
Motor neuropathy (n=32)	0 (0-3)
Sensory neuropathy (n=35)	1 (0-4)
Neuropathic pain (n=34)	1 (0-3)

SEM = standard error of the mean; NRS = numerical rating score; CTC = common toxicity criteria

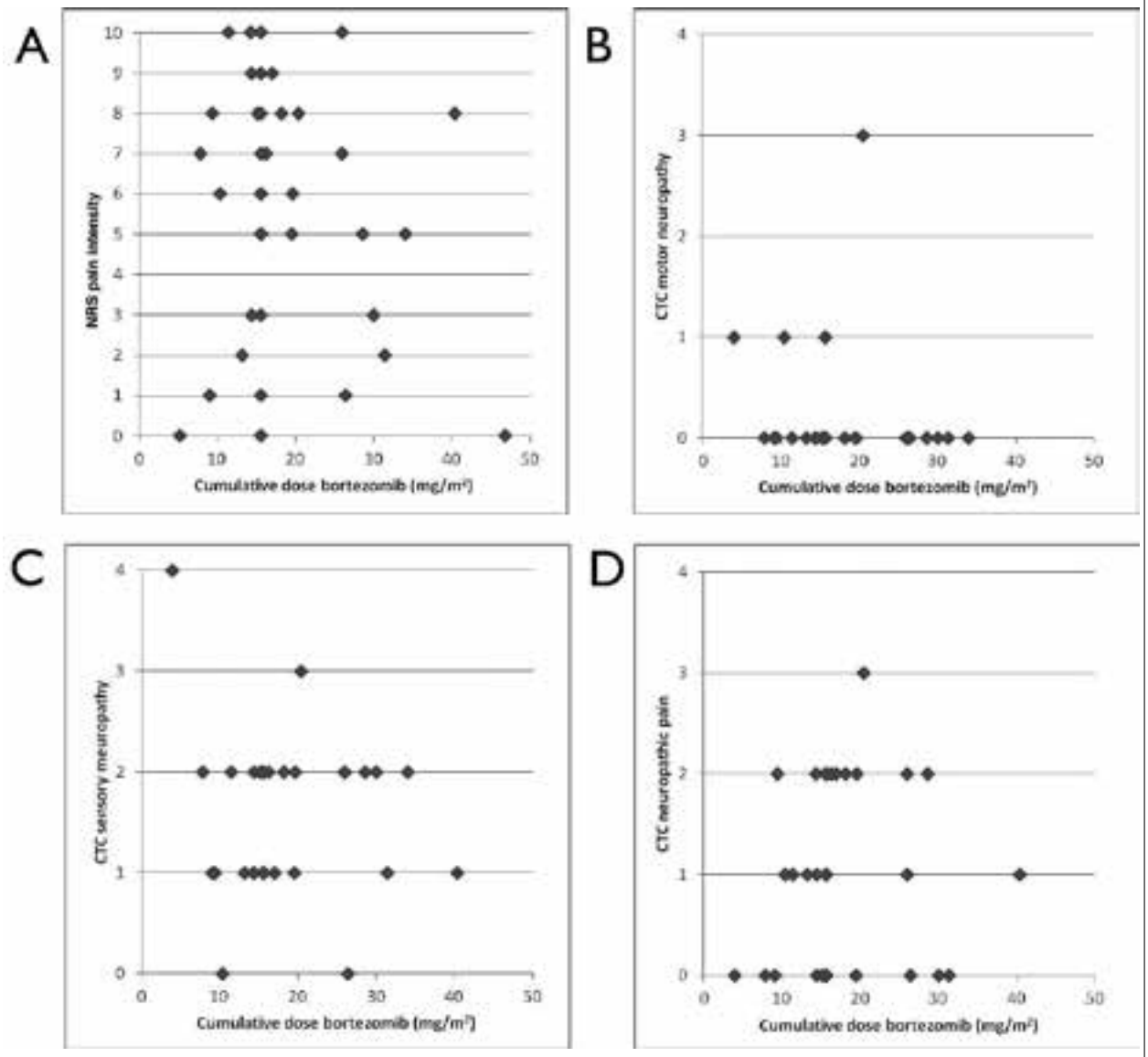
the score list, medians for the separate CTC groups and median NRS pain intensity. In this patient population there is no linear correlation between cumulative dose and NRS pain intensity or the individual CTC subgroups (*figure 1A-D*); nor between dose intensity and NRS pain intensity/CTC.

In 23 patients the dosage regimen of bortezomib was modified because of symptoms of polyneuropathy. In nine patients (27.3%) the dose was reduced and in 17 patients (51.5%) bortezomib treatment eventually had to be discontinued. In ten patients dosage regimen was unchanged and in six patients the exact dosage regimen of bortezomib could not be retrieved from the clinical records. Noteworthy, in 21 patients pain severity initially increased after cessation of bortezomib.

Of the 27 patients with NRS pain intensity of 5 or higher, 23 used one or more analgesic drugs: 22 used antiepileptic drugs (pregabalin or gabapentin), 7 antidepressants (amitriptyline) and 11 opioids (tramadol, morphine or oxycodone). In 16 patients a follow-up NRS pain intensity was known. Eventually in all of these cases at least a 30% reduction in pain was reached after a median of 64 days (range 18-430).

Because of differences in the bortezomib dosage regimen between previously untreated and treated patients, we were unable to perform an analysis of the effects of previous

Figure 1. *Correlation between cumulative dose of bortezomib and A) NRS pain intensity, B) CTC motor neuropathy, C) CTC sensory neuropathy, and D) CTC neuropathic pain*



NRS = numerical rating score, CTC = common toxicity criteria.

Table 3. *Nerve conduction studies*

	Normal	Abnormal	Missing
Median nerve (sensory)	14	7	5
Ulnar nerve (sensory)	9	15	2
Sural nerve (sensory)	6	14	6
Ulnar nerve (motor)	8	10	8
Peroneal nerve (motor)	16	8	2

treatment with neurotoxic chemotherapy on NRS pain intensity and CTC scores.

In 26 patients NCS at the time of bortezomib-induced polyneuropathy were available (*table 3*). In most patients a predominantly sensory (n=9) or mixed axonal polyneuropathy (n=12) was found. There was no clear correlation between EMG abnormalities and severity of the pain. Most striking were three patients with severe pain (NRS pain intensity score 8 or 9) and completely normal findings on the EMG. Additionally, in ten patients NCS had also been performed before initiation bortezomib treatment. Two of them were not previously treated with neurotoxic chemotherapy and had normal baseline NCS that deteriorated during treatment with bortezomib to a sensory and mixed polyneuropathy with a pain score of 6 and 7 respectively. Six out of the eight previously treated patients had abnormal NCS. Two patients who were previously treated with thalidomide had normal baseline NCS; in one of them it remained normal, despite developing a pain score of 9 during treatment with bortezomib.

DISCUSSION

Bortezomib is a proven effective treatment for multiple myeloma, whose frequently occurring painful polyneuropathy is an important dose-limiting side effect. This polyneuropathy typically occurs rather early during treatment. In our group, the first symptoms of polyneuropathy developed after a median time of 67 days, which is similar to a previously reported duration of 42 days to 2.5 months.[7,8,10]

More than two-thirds of the patients in our cohort had a pain score of 5 or more, i.e. moderate to severe pain.[17,18] Although most authors mention pain as a prominent symptom, there is only one other study which actually quantified pain by means of NRS.[19] In this prospective study on multiple myeloma patients who developed bortezomib-induced polyneuropathy, the percentage of patients with pain (less than 25%) was lower than in our study. In another study the percentage of patients who experienced pain during treatment with bortezomib varied between 50% for previously untreated patients and 81% in previously treated patients.[8]

We did not find a clear linear correlation between the cumulative dose or dose intensity and severity of polyneuropathy, indicating that some patients developed a severe polyneuropathy after a relatively low dose of bortezomib and vice versa. A phase II study with patients who received previous chemotherapy,[20] and two recent phase III trials, with both previously treated and chemotherapy-naive patients with multiple myeloma,[7,9] all showed that the risk of developing bortezomib-induced polyneuropathy did not increase above a cumulative dose of 30-45 mg/m^2, confirming the absence of linear dose-toxicity.

Although often bortezomib-induced neuropathic pain is severe and prolonged, most patients improve over time. In the majority of patients in our cohort bortezomib dosage was adjusted and various medications against neuropathic pain were prescribed to reduce pain. These data confirm the general view that bortezomib-induced polyneuropathy has a favourable outcome regarding symptoms,[1,9,20] provided that the dose is adjusted in time to prevent progression of symptoms. Currently a validated algorithm based on CTC criteria for the severity of the neuropathy is used.[7] Recently an even stricter guideline was proposed, which recommends dose adjustment when symptoms regarding neuropathic pain first occur and are still minimal.[21] The rationale is that once severe symptoms have developed resolution takes more time and therefore the occurrence of severe symptoms must be prevented.

Different dosage regimens appear to influence the incidence of bortezomib-induced polyneuropathy. Recent investigations regarding the effectiveness of bortezomib in treating multiple myeloma showed a lower incidence of bortezomib-induced polyneuropathy with subcutaneous administration and less intensive dosage regimen (for example, once instead of twice weekly).[22-24]

Symptomatic treatment is still empirical in the absence of specific studies on the effectiveness of neuropathic analgesics in bortezomib-induced polyneuropathy. Studies investigating possible neuroprotective medication for the prevention of bortezomib-induced polyneuropathy have not been conclusive.[25]

A pre-existent polyneuropathy, for example caused by diabetes mellitus, excessive alcohol use or multiple myeloma, has been shown to be a risk factor for developing bortezomib-induced polyneuropathy.[6,9] Many multiple myeloma patients receive different potentially neurotoxic agents (vincristine, thalidomide). In our cohort we could not assess a predisposing effect of this previous treatment on the development of bortezomib-induced polyneuropathy, because of differences in dosage regimen between previously treated and untreated patients. Some studies found no clear link between previous neurotoxic chemotherapy and the emergence of bortezomib-induced

polyneuropathy.[6,7,20,26] In contrast, others described that patients who had previously used neurotoxic chemotherapy could be at an increased risk to develop neuropathic pain during treatment with bortezomib.[8,19,27]

A direct comparison between these neurotoxic drugs is difficult because of clinical and pathophysiological differences. Thalidomide-induced polyneuropathy is a predominantly sensory, dose- and duration-dependent polyneuropathy with both clinical and neurophysiological evidence for axonal involvement.[28] The data on vincristine-induced polyneuropathy, a sensorimotor, duration-dependent neuropathy, are also consistent with direct axonal toxicity. Pathophysiologically microtubules are involved, though the exact mechanism is still not fully clarified.[29]

Contrary to the axonal neuropathies caused by thalidomide and vincristine, bortezomib-induced polyneuropathy is a small diameter neuronopathy. In an animal model bortezomib mainly caused toxicity to the dorsal root ganglia, Schwann cells and myelin and axonal damage to a lesser extent.[30] Genetic studies also identified a different set of genes for bortezomib-induced polyneuropathy compared with vincristine-induced polyneuropathy suggesting different molecular mechanisms.[10]

No correlation was found in our cohort between the severity of pain and severity of abnormalities in NCS. Some patients with much pain had normal NCS. This implies that conventional NCS have limited diagnostic value. This is probably explained by the fact that pain is an expression of small fibre damage and NCS are not an adequate tool for evaluation these fibres. One other study described small fibre neuropathy due to bortezomib using quantitative sensory testing, which may be more sensitive for the detection of small fibre dysfunction than NCS.[31]

In conclusion, bortezomib-induced polyneuropathy is a common, painful and dose-limiting side effect, however with a favourable outcome if bortezomib treatment is adjusted timely. It is therefore advisable to establish an accurate clinical neurological diagnosis and to follow-up symptoms of polyneuropathy, specifically paraesthesias and (neuropathic) pain. This should be done during and preferably also before initiation of treatment with bortezomib. Since bortezomib-induced polyneuropathy preferentially affects small diameter nerve fibres, conventional NCS are of limited additional value. The history of the patient and the severity of complaints are the decisive factors in the management of this sometimes severe iatrogenic complication.

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Appendix. *Score list to assess the severity of chemotherapy-induced polyneuropathy*[11,12]

	Absence/presence
Paresthesias	0/1
Numbness	0/1
Loss of dexterity	0/1
Unsteadiness of gait	0/1
	Normal/abnormal
Position sense hallux	0/1
Vibration sense hallux	0/1
Pin-prick sensation hallux	0/1
Romberg's sign	0/1
Romberg's sign with heel-to-toe stand	0/1
Knee tendon reflexes	0/1
Ankle tendon reflexes	0/1
Total	0-11