Bortezomib-induced peripheral neurotoxicity: still far from a painless gain

Guido Cavaletti,* Eduardo Nobile-Orazio°

**Department of Neurosciences and Biomedical Technologies, University of Milan "Bicocca", Monza; °Department of Neurological Sciences, University of Milan; 2nd Neurology, IRCCS Humanitas Clinical Institute, Rozzano, Milan, Italy.*
E-mail: guido.cavaletti@unimib.it. *DOI: 10.3324/haematol.11752*

Inhibition of protein degradation through the ubiquitin–proteasome pathway is a recently developed approach to cancer treatment that adds to the range of cellular targets for chemotherapy (DNA, the cytoskeleton, and transcription and replication enzymes).[1] The proteasome carries out the regulated degradation of unnecessary or damaged cellular proteins; the array of proteins targeted by the proteasome include those that regulate cell-cycle progression and apoptosis. On May 13th, 2003 the U.S. Food and Drug Administration granted accelerated approval for the use of the 20S proteasome complex inhibitor bortezomib as a single agent for the treatment of patients with multiple myeloma after two prior therapies and progressing on their most recent treatment. Two years later bortezomib received regular approval for the treatment of multiple myeloma progressing after at least one prior therapy. In Europe an approval under *exceptional circumstances* was granted in January 2004 by the European Medicines Agency (EMEA) pending an annual reassessment of the benefit-risk balance.

Since the first phase I trial it appeared that, among the major dose-limiting toxicities, sensory neurotoxicity was particularly relevant.[2,3] The two pivotal phase II trials included a total of 256 patients (228 of whom were treated with the 1.3 mg/m^2 dose) and used the same schedule of twice-weekly intravenous boluses of bortezomib for 2 weeks every 21 days for up to eight cycles. Peripheral neuropathy was reported in 37% of these patients, while grade 3 peripheral neuropathy occurred in 14% of them. In the study on 202 patients reported by Richardson *et al*.[4] all the patients had been heavily pretreated. Among the 33 patients who did not have neuropathy before beginning bortezomib therapy, grade 3 neuropathy developed in one and grade 1 or 2 neuropathy developed in 16.

Overall, 12% of the patients required a reduction of the dose at least once, and 4% of patients discontinued treatment because of peripheral neuropathy. The authors concluded that «the most clinically significant adverse event was cumulative, dose-related peripheral sensory neuropathy», although they suggested that «the incidence of neuropathy will be lower in ongoing clinical trials of bortezomib involving patients with earlier-stage myeloma who do not have preexisting neuropathy». However, in the trial reported by Jagannath *et al*.,[5] 54 patients were treated with two different bortezomib doses (i.e. 28 of them with 1.0 mg/m^2 and 26 with 1.3 mg/m^2) and the cumulative incidence of severe peripheral neuropathy was 9% (grade 4 in one case). Treatment-emergent neuropathy of any grade was reported in 41% of patients, a rate very close to that observed in the population with more advanced disease reported by Richardson *et al*.[4] To explain this rather disappointing result the authors evidenced that a large proportion of the patients had entered the study with baseline signs of neuropathy. In both studies it was reported that a striking feature of bortezomib-induced peripheral neurotoxicity was neuropathic pain, a symptom rarely reported as severely disabling with other neurotoxic antineoplastic drugs, and that recovery occurred in most patients within months after withdrawal of treatment. These data about the incidence, severity and clinical features of bortezomib-induced peripheral neurotoxicity were substantially confirmed by subsequent studies of patients with hematologic malignancies.[3,6-14] Given the anticancer effectiveness of bortezomib, the issue of peripheral neuropathy in pretreated patients was specifically addressed.[15] Despite possible limitations which could prevent the generalization of their results, the authors concluded that peripheral neuropathy seems to be a cumulative, dose-related adverse effect and that its prevalence increases through the first five treatment cycles. More than two-thirds of the patients with clinically significant neuropathy experienced resolution or improvement of neuropathic pain and other symptoms during treatment after dose modification or on completion of therapy. However, peripheral neuropathy was dose-limiting in 5% of the patients and dose reduction was required in 12% of the treated subjects.

In this analysis, the development of treatment-emergent peripheral neuropathy was reported to be independent of the type of prior neurotoxic therapy that the patient had received and the presence and severity of pre-existing neuropathy. Dose modifications have been suggested in order to limit the onset of bortezomib-induced peripheral neurotoxicity.[15]

The risk of developing clinically relevant peripheral neurotoxicity was not changed by the use of bortezomib as first-line therapy. In fact, when it was used as first-line treatment in multiple myeloma, drug administration was discontinued because of peripheral neurotoxicity in 4% of the patients, with the incidence of peripheral neuropathy being 30% (6% grade 3) in one study,[16] while 31% of the patients had grade 2 or higher (16% grade 3) peripheral neuropathy in another study.[17] Again, no associated risk factors for the development of severe bortezomib-induced

peripheral neuropathy have been clearly established. Age >75 years was indicated as an additional risk factor for the onset of bortezomib-induced peripheral neurotoxicity when the drug was used as first-line treatment, since the incidence of grade 3/4 peripheral neuropathy was 14% in the youngest patients and 25% in the oldest ones;[18] however, given the relatively low number of patients this conclusion should further be confirmed.

A further alert and strong indication to carefully investigate the peripheral neurotoxicity of bortezomib come from a recent study reported by Chen *et al*.[19] of treatment-naïve or previously treated patients with Waldenström's macroglobulinemia. In fact, in this small study 74% of the patients developed new or worsening peripheral neuropathy (grade 3 and dose-limiting in 18% of the patients), generally early in the course of the treatment. Most of the affected patients had a complete or partial recovery from pain and neuropathy-related symptoms, although recovery required up to 2 years. Interestingly, in this study motor neuropathy was reported in a minority of the patients, in addition to the typical sensory, painful neuropathy.

Finally, with an increasing number of patients exposed to bortezomib, uncommon presentations of neuropathy during treatment, such as severe autonomic or motor neuropathy,[20] have been occasionally reported during scientific meetings, although it should be stressed that a causal relationship with drug administration has never been clearly demonstrated (*personal communications and observations*). It also remains unclear whether the long-term use of bortezomib may cause additional complications due to protracted inhibitory effects on proteasome cleavage of pathological proteins.

All these data have recently led the EMEA to announce some relevant modifications, mainly related to neurotoxicity, in the next Product Information sheet, including the obligation for «patients experiencing new or worsening peripheral neuropathy» to «undergo neurological evaluation» and the anticipated reduction of the dose of bortezomib related to both sensory and motor neuropathy.

From a review of the available data it is clear that the current knowledge on the clinically relevant features of bortezomib-induced peripheral neurotoxicity needs to be substantially improved. In fact, the effectiveness of this compound is so impressive and the potential benefit for the patients is so great that every effort should be made to prevent this dose-limiting effect and to increase the safety of this drug. One major issue is that it is unclear how and to what extent proteasome inhibition can damage the peripheral nervous system. In this perspective, the availability of an animal model of bortezomib-induced peripheral neurotoxicity[21] might be helpful to investigate the pathogenesis of this drug-related complication. In fact, the finding that dorsal root ganglia and peripheral nerve glial cells, and not only axons, can be damaged by bortezomib at doses which induce the same extent of proteasome inhibition detected during the clinical use of the drug allows unexpected speculations on the mechanism of the peripheral neurotoxicity. Moreover, animal models might also be useful to test strategies, besides dose modification, to prevent or reduce such neuropathy. However, only prospective and carefully designed studies on homogeneous, large series of patients treated first-line with the drug might be able to establish clearly the clinical features of bortezomib-peripheral neurotoxicity, identify subjects at high risk of developing this side effect and determine the extent and time course of recovery from this complication. Standardized neurophysiological testing will also be extremely helpful to identify the target of bortezomib toxicity in the peripheral nervous system, since the few data reported so far are inconclusive and experimental results suggest that involvement of the peripheral nervous system might be more relevant than previously believed.[21,22]

For all these reasons, until there is more precise knowledge on bortezomib-induced peripheral neurotoxicity and in view of the possible combined use with other neurotoxic drugs, a prudent attitude is advisable, careful monitoring of the patients is necessary, and collaboration among clinicians and researchers is mandatory; accurate reporting of uncommon cases will probably also be very useful. Finally, continuous reassessments of the Product Information sheet should be supported and oncologists should be encouraged to comply with the Agency's recommendations.

References

1. San Miguel J, Blade J. Perspective on the current use of bortezomib in multiple myeloma. Haematologica 2006; 91:871-2.
2. Aghajanian C, Dizon DS, Sabbatini P, Raizer JJ, Dupont J, Spriggs DR. Phase I trial of bortezomib and carboplatin in recurrent ovarian or primary peritoneal cancer. J Clin Oncol 2005;23:5943-9.
3. Orlowski RZ, Voorhees PM, Garcia RA, Hall MD, Kudrik FJ, Allred T, et al. Phase 1 trial of the proteasome inhibitor bortezomib and pegylated liposomal doxorubicin in patients with advanced hematologic malignancies. Blood 2005;105:3058-65.
4. 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: 2609-17.
5. 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;127:165-72.
6. Berenson JR, Yang HH, Sadler K, Jarutirasarn SG, Vescio RA, Mapes R, et al. Phase I/II trial assessing bortezomib and melphalan combination therapy for the treatment of patients with relapsed or refractory multiple myeloma. J Clin Oncol 2006;24:937-44.

7. Bruno B, Patriarca F, Sorasio R, Mattei D, Montefusco V, Peccatori J, et al. Bortezomib with or without dexamethasone in relapsed multiple myeloma following allogeneic hematopoietic cell transplantation. Haematologica 2006; 91:837-9.
8. Faderl S, Rai K, Gribben J, Byrd JC, Flinn IW, O'Brien S, et al. Phase II study of single-agent bortezomib for the treatment of patients with fludarabine-refractory B-cell chronic lymphocytic leukemia. Cancer 2006;107:916-24.
9. Fisher RI, Bernstein SH, Kahl BS, Djulbegovic B, Robertson MJ, de Vos S, et al. Multicenter phase II study of bortezomib in patients with relapsed or refractory mantle cell lymphoma. J Clin Oncol 2006;24:4867-74.
10. Goy A, Younes A, McLaughlin P, Pro B, Romaguera JE, Hagemeister F, et al. Phase II study of proteasome inhibitor bortezomib in relapsed or refractory B-cell non-Hodgkin's lymphoma. J Clin Oncol 2005;23:667-75.
11. Kropff MH, Bisping G, Wenning D, Volpert S, Tchinda J, Berdel WE, et al. Bortezomib in combination with dexamethasone for relapsed multiple myeloma. Leuk Res 2005; 29:587-90.
12. Musto P, Falcone A, Sanpaolo G, Guglielmelli T, Zambello R, Balleari E, et al. Bortezomib (Velcade) for progressive myeloma after autologous stem cell transplantation and thalidomide. Leuk Res 2006;30:283-5.
13. O'Connor OA, Wright J, Moskowitz C, Muzzy J, MacGregor-Cortelli B, Stubblefield M, et al. Phase II clinical experience with the novel proteasome inhibitor bortezomib in patients with indolent non-Hodgkin's lymphoma and mantle cell lymphoma. J Clin Oncol 2005;23:676-84.
14. Palumbo A, Ambrosini MT, Benevolo G, Pregno P, Pescosta N, Callea V, et al. Bortezomib, melphalan, prednisone and thalidomide for relapsed multiple myeloma. Blood 2007;109:2767-72.
15. Richardson P, Jagannath S, Colson K. Optimizing the efficacy and safety of bortezomib in relapsed multiple myeloma. Clin Adv Hematol Oncol 2006;4:1.
16. 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;91:1498-505.
17. 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;129:776-83.
18. 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 I/II study. Blood 2007;108:2165-72.
19. Chen CI, Kouroukis CT, White D, Voralia M, Stadtmauer E, Stewart AK, et al. Bortezomib is active in patients with untreated or relapsed Waldenstrom's macroglobulinemia: a phase II study of the National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol 2007;25:1570-5.
20. Gupta S, Pagliuca A, Devereux S, Mufti GJ, Schey S. Life-threatening motor neurotoxicity in association with bortezomib. Haematologica 2006;91:1001.
21. 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;204:317-25.
22. Cata JP, Weng HR, Burton AW, Villareal H, Giralt S, Dougherty PM. Quantitative sensory findings in patients with bortezomib-induced pain. J Pain 2007;8:296-306.