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REVIEW ARTICLE

Bortezomib-induced peripheral neurotoxicity: an update

Andreas A. Argyriou · Guido Cavaletti · Jordi Bruna · Athanasios P. Kyritsis · Haralabos P. Kalofonos

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Abstract This review paper provides a critical exploration of updates concerning the spectrum of characteristics and treatment options of bortezomib-induced peripheral neuropathy (BIPN). Emphasis is given on pathogenesis issues. Although the mechanism underlying BIPN still remains elusive, it is increasingly acknowledged that the inhibition of proteasome activity in dorsal root ganglia and peripheral nerves, the mitochondrial-mediated disruption of Ca^{++} intracellular homeostasis and the disregulation in nuclear factor κB and brain-derived neurotrophic factor play a significant pathogenic role. Assessment of BIPN is based on comprehensive grading scales, using a combination of "subjective" and "objective" parameters, which turn out to be ambiguously interpreted, thus leading to both under- and misreporting of its true incidence and severity. BIPN is clinically defined as a typical example of a dose-dependent, distally attenuated painful, sensory neuronopathy. Patients pre-treated with neurotoxic regimens and those with pre-existing neuropathy are more likely to develop severe neurotoxicity. To date, there is no effective pharmacological treatment to prevent BIPN, and therefore, interventions remain merely symptomatic to focus on the alleviation of neuropathic pain. Hence, strict adherence to the dose reduction and schedule change algorithm is recommended in order to prevent treatment-emergent BIPN and allow the continuation of treatment. Further studies in animal models and humans, including experimental, clinical, neurophysiological and pharmacogenetic approaches, are needed to allow the identification of the true spectrum of BIPN pathogenesis and characteristics. It is expected that such comprehensive approaches would be the starting point for the development of early preventive and therapeutic interventions against BIPN.

Keywords Bortezomib · Peripheral neuropathy · Neurotoxicity · Pathogenesis · Diagnosis · Incidence · Treatment

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Introduction

The ubiquitin proteasome system (UPS) is the principal cellular pathway to regulate intracellular protein degradation, and this task is performed by a complex proteolytic machine, composed of several components. Soon after the identification of the characteristics of UPS in the early 1980s, there were several attempts to selectively induce apoptosis in tumour cells with the development of novel proteasome inhibitors (Shen et al. 2013).

Bortezomib (BTZ), a boronic acid dipeptide 20S proteasome complex inhibitor, was approved in 2004 by both US

and European authorities for the treatment of multiple myeloma (MM) and mantle cell non-Hodgkin's lymphoma. The antitumour action of BTZ is based on its ability to induce G_2-M cell cycle arrest, apoptosis by causing Bcl-2 phosphorylation, inhibition of NF-κB and eventually inhibition of angiogenesis (Piperdi et al. 2011).

Chemotherapy-induced peripheral neurotoxicity (CIPN) ranks among the most common non-haematological and dose-limiting toxicities of a number of effective chemotherapeutic agents, including taxanes, platinum compounds and proteasome inhibitors such as BTZ, administered either alone or in combination regimens (Argyriou et al. 2007; Sioka and Kyritsis 2009). In this context, bortezomib-induced peripheral neuropathy (BIPN) is considered to be one of the most severe, unpredictable and potentially permanent non-haematological side effects of chemotherapy against MM, thus also having a detrimental effect on the quality of life (QoL) of survivors (Argyriou et al. 2008, 2010). This is because patients with pre-existing peripheral neuropathy or those at high risk might be treated with subcutaneous BTZ as it appears to be less neurotoxic than BTZ when administered intravenously (Argyriou et al. 2012, 2014). This review study provides a critical exploration of updates relating to the pathogenesis, clinical characteristics and management of BIPN.

The ubiquitin proteasome system (UPS)

The cytosolic 26S proteasome (approximately 2,000 kDa in molecular mass) is composed by one 20S protein subunit and two 19S regulatory cap subunits. The core where protein degradation is eventually completed is hollow with openings at the two ends, which are associates with a 19S regulatory subunit each, containing multiple ATPase active sites and ubiquitin-binding sites. This structure recognizes polyubiquitinated proteins and transfers them to the catalytic core. Although both 26S and 20S proteasomes have proteolytic activity (Finley 2009), 26S proteasome activity is required for normal neuronal homeostasis, while 20S proteasome is insufficient for neuronal survival (Bedford et al. 2008). In mammals, 20S core particle is formed by α and β subunits, divided into 4 concentric rings. The outer two rings in the stack consist of seven α subunits each, which serve as docking domains for the regulatory activity. The inner two rings each consist of seven β subunits each and contain the protease active sites that perform the proteolysis reactions. The β1, β2 and β5 subunits are catalytic, with three distinct substrate specificities considered chymotrypsin-like, trypsin-like and peptidyl-glutamyl peptide-hydrolyzing.

BTZ primarily targets the β5 and, to a lesser extent, the β1 proteasome subunits (Adams 2004; Richardson et al. 2006a). The mechanism of BTZ anticancer activity has been extensively investigated, and it has been demonstrated that its main signalling pathways include the up-regulation of genes involved in pro-apoptotic pathways, inhibition of NF-κB activation, induction of endoplasmic reticulum stress and activation of the mitochondrial-based ("intrinsic") apoptotic pathway, which lead to cell cycle arrest and apoptosis (McConkey and Zhu 2008).

Pathogenesis of peripheral neuropathy

In well-characterized animal models of BIPN, it has been demonstrated that the administration of BTZ using neurotoxic schedules remarkably inhibits proteasome activity in dorsal root ganglia (DRG) and peripheral nerves, although the dynamics and extent of this inhibition are different, while it is confirmed that no effect is present in the brain (Meregalli et al. 2014). However, given the important differences in the biology of cancer cells and neurons, it is not established whether the same mechanisms at the basis of BTZ anticancer activity are also responsible for its neurotoxicity, although mitochondrial and endoplasmic reticulum damage in both Schwann and satellite cells (Fig. 1a, b) has been observed in the sciatic nerve and DRG of mice and rats treated with BTZ (Cavaletti et al. 2007; Bruna et al. 2010, 2011).

Moreover, the observation that BIPN is more severe in patients affected by multiple myeloma (MM) than in subjects treated with BTZ due to solid cancers (Roccaro et al. 2006) increases the possibility that MM itself plays a role in the genesis of BIPN. In fact, it is well recognized that more than 50 % of MM patients have neurophysiologically evident abnormalities at baseline and this comorbidity might enhance the neurotoxicity of BTZ through still unknown mechanisms (Richardson et al. 2009a).

On this background, several experimental studies have been performed and suggested events and mechanisms which are likely to be relevant to the onset and course of BIPN besides cytoplasmic proteasome inhibition (Broyl et al. 2012). Intracellular calcium homeostasis disruption in BTZ-treated subjects can have detrimental effects on mitochondrial activity (Landowski et al. 2005), but also induce changes in nerve activity, promoting depolarization and spontaneous discharge, which might be at the basis of the typical neuropathic pain reported by BTZ-treated patients (Siau and Bennett 2006).

Axonal excitability has been tested in patients treated with BTZ using the threshold tracking technique (Bostock et al. 1998; Kiernan and Bostock 2000), a sophisticated neurophysiological method able to detect aberrant axonal function prior to the development of pathological changes detected using conventional techniques. In a small cohort

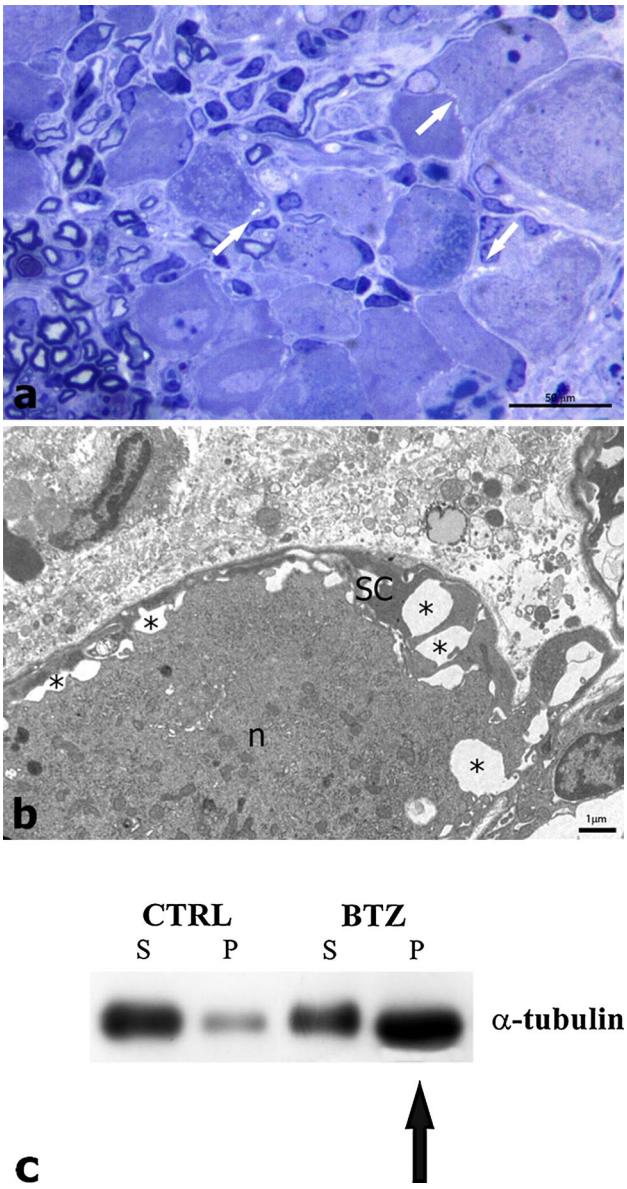

Fig. 1 Dorsal root ganglion light micrograph obtained from a bortezomib-treated rat. Neurons have a normal aspect, while satellite cells show mild intracytoplasmic vacuolations (*arrows*). Electron micrograph showing severe vacuolation (*asterisks*) in the cytoplasm of a satellite cell (sc) surrounding a neuron (n) of normal aspect. Representative immunoblot demonstrating a marked shift from the soluble (S) to the polymerized (P) form of α-tubulin in the sciatic nerve of a bortezomib-treated (BTZ) rats vs a control animal (CTRL)

of patients treated with BTZ sensory axonal, excitability indices, superexcitability and depolarizing threshold electrotonus significantly decreased immediately after the first cycle of treatment, and these changes persisted until completion of the third cycle. On the motor side, excitability testing showed significantly decreased depolarizing threshold electrotonus after the second cycle of treatment. However, despite the recognition of these changes in nerve fibre excitability, no significant differences between the magnitude of excitability changes and the severity of chronic BIPN could be evidenced (Nasu et al. 2014). The observed axonal membrane depolarization suggests plasma membrane ion flow dysfunction, possibly related to decreased Na^+–K^+-ATPase-dependent pump function, or altered Na^+ or K^+ conductance (Han et al. 2008; Kiernan and Bostock 2000; Kiernan et al. 2000) and a continuous and abnormal influx of Na^+ ions can cause overload of the Na^+–K^+-ATPase-dependent pump, resulting in the initiation of mitochondrial energy conversion failure, as well as in other alterations in intracellular ion concentrations (Nodera et al. 2011; Waxman 2008). Given several methodological limitations (firstly, the very small cohort of patients investigated), the intriguing results of this clinical study need further confirmation.

Recent studies evidenced another intracellular target of BTZ activity that might be relevant to BIPN, i.e. tubulin. In in vitro experiments, Poruchynsky and colleagues (Poruchynsky et al. 2008) demonstrated that BTZ is able to increase the amount of polymerized tubulin polymerization and to induce microtubule stabilization in several cell types. Interestingly, not only cancer cells (e.g. neuroblastoma, MM cells) but also neurons are sensitive to this BTZ, although the extent of the effect was different. To investigate in vivo the relevance of BTZ-induced tubulin polymerization in the pathogenesis of BIPN, this phenomenon was analysed using a well-characterized chronic rat model (Meregalli et al. 2010, 2012). In this model, the kinetics and extent of proteasome inhibition and of tubulin polymerization were evaluated and correlated with different BIPN features. It showed that BTZ induced tubulin polymerization in the sciatic nerves (Fig. 1c) and DRG, while this effect was not evident in the brain, and that it was closely with BIPN severity. Similar results were confirmed in vitro in different experimental settings (Staff et al. 2013; Meregalli et al. 2014).

Besides its effects in the cytoplasm, BTZ also has marked effects at the nuclear level, where nuclear processes are organized in structural and functional compartments (Palanca et al. 2014). Within the nucleus, proteasomal proteolysis is involved in quality control mechanisms and in the turnover and activity of nuclear proteins such as transcription regulators and splicing factors (Desterro et al. 2000; Lafarga et al. 2002; von Mikecz 2006), all events that might be affected by BTZ activity. In fact, it has been demonstrated in DRG neurons of BTZ-treated rats (Casafont et al. 2010) that the inhibition of proteasome activity induces accumulation of ubiquitinated proteins, reduction of extranucleolar transcription and nuclear retention of polyadenylated RNAs in nuclear bodies called poly(A) granules. These results were subsequently expanded, also demonstrating changes in the geometry, position and polarity of

the neuronal nucleus, associated with disruption of the protein synthesis mechanism and DNA damage (Palanca et al. 2014). However, these marked changes were not associated with DRG neuronal death, in agreement with previously reported in vivo observations (Carozzi et al. 2010; Meregalli et al. 2010; Bruna et al. 2010; Carozzi et al. 2013; Chiorazzi et al. 2013).

Extracellular factors possibly involved in BIPN include autoimmune factors and inflammation (Ravaglia et al. 2008; Alé et al. 2014) and blockade of nerve growth factor-mediated neuronal survival secondary to BTZ-mediated inhibition of the activation of nuclear factor κB (NF-κB) (Richardson et al. 2003). Changes in brain-derived neurotrophic factor (BDNF) levels have recently been proposed as a candidate mechanism underlying BIPN (Broyl et al. 2010). In this context, it should be considered that platelets play an important role in the homeostasis of BDNF in the blood, since BDNF is stored and transported in human platelets and released by agonist stimulation (Fujimura et al. 2002).

A clinical study tested the hypothesis that decreased BDNF levels in the plasma of patients with BIPN may result from a lack of secretion of the growth factor from the platelets, even in patients without a decrease in their blood count (Azoulay et al. 2014). In this study, flow cytometric analysis evidenced an increase of BDNF content in the platelets of patients with BIPN compared to platelets of patients without BIPN. Although altered peripheral blood levels of BDNF were associated with neurological impairment (Azoulay et al. 2005), these results suggest that mechanisms involving BDNF release might act in BTZ-treated patients. In fact, platelet aggregation is inhibited by exposure to BTZ (Avcu et al. 2008) and platelets from MM patients treated with BTZ have diminished aggregation in response to several agonists (Zangari et al. 2008). By reducing platelet activation, BTZ might inhibit BDNF release from its main storage compartment, therefore depriving nerve fibres and neurons of its trophic support during the onset of BIPN and limiting the possibility of effective repair.

Although the neurotoxicity mechanism of BTZ remains to be elucidated, the results obtained so far indicate that investigation is still necessary to understand the pathogenesis of BIPN, also considering intracellular targets other than the proteasome.

Diagnosis

The diagnosis of BIPN is established in most of the relevant studies with the use of standard clinical grading scales, such as the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAEv3 or v4 for sensory and motor neuropathy) and the 11-item neurotoxicity subscale [FACT/GOG-Ntx (Functional Assessment of Cancer Therapy/Gynaecologic Oncology Group-Neurotoxicity)] that was developed by the Gynaecologic Oncology Group (Cavaletti et al. 2010).

To overcome limitations in accurately grading BIPN with those scales resulting from intra- and interobserver variation (Postma et al. 1998), some recently published studies have also employed either the Total Neuropathy Score (TNS) or shorter variants, such as the reduced (TNSr) or clinical (TNSc) version of TNS (Lanzani et al. 2008; Velasco et al. 2010; Zaroulis et al. 2014). Recent evidence from our group showed that the TNSc appears superior to NCI-CTCAE in terms of sensitivity in estimating the severity of CIPN, including BIPN (Cavaletti et al. 2013). As such, we recommend the use of TNSc to assess BIPN, but for a comprehensive evaluation, patients should also be tested with the pain Visual Analogue Scale (VAS) or the 11-point pain intensity numerical scale (PI-NRS), to capture the intensity of neuropathic pain in the context of BIPN.

Incidence and severity of BIPN

According to the results of major phase 2/3 clinical trials, as outlined in Table 1, the incidence of BIPN ranges from 31 to 45 %. First-line BTZ treatment administered in the usual manner (intravenous administration of bortezomib 1.3 mg/m^2, twice a week for 2 weeks, followed by 1 week without treatment) is able to induce grade 1 or 2 BIPN in 14 and 17 % of treated patients, respectively, when assessed with the NCI-CTCAE scale.

Pre-treatment with other neurotoxic antineoplastic drugs, such as vincristine and thalidomide, is associated with even higher percentages (18–37 %) of clinically significant (grades 1 and 2) BIPN. In those pre-treated patients, included in Table 1 ($n = 2{,}174$ patients), the incidence rate of treatment emergent, severe (grades 3 and 4) neurotoxicity following administration of intravenous (iv) BTZ at 1.3 mg/m^2 per dose and at weighted arithmetic cumulative received mean dose of 28.5 mg/m^2 is about 7 %. These severe BIPN incidence estimates are comparable (9 %) to those observed in patients ($n = 855$ patients) receiving first-line BTZ treatment, although those newly treated MM patients had received a higher weighted arithmetic cumulative mean dose of 40.5 mg/m^2. Dose reduction or treatment discontinuation occurs in up to 12 % of BTZ-treated patients due to treatment-emergent BIPN, mostly occurring in those with pre-existing neuropathy due to exposure to other neurotoxic chemotherapies (Richardson et al. 2006b; Garderet et al. 2012; Dimopoulos et al. 2011).

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