Bortezomib-induced peripheral neurotoxicity: An update.

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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.

Key words:

Bortezomib, peripheral neuropathy, neurotoxicity, pathogenesis, diagnosis, incidence, treatment

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 proteosome inhibitors (Shen et al. 2013).

Bortezomib (BTZ), a boronic acid dipeptide 20S proteosome 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 antitumor 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-kB 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 proteosome inhibitors such as BTZ, either administered 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; Argyriou et al. 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; Argyriou et al. 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 (approx. 2000 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 if 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; Bruna et al. 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 co-morbidity 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 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 analyzed using a well-characterized chronic rat model (Meregalli et al. 2010; Meregalli et al. 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 organised in structural and functional compartments (Palanca et al. 2013). 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. 2013). 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. In press) and blockade of nerve growth factor-mediated neuronal survival secondary to BTZ-mediated inhibition of the activation of nuclear factor κB (NFκB) (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. In press). 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 (grade 1 and 2) BIPN. In those pre-treated patients, included in table 1 (n=2174 patients), the incidence rate of treatment emergent, severe (grade 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).

On the other hand, and as shown in table 1, BTZ used as induction pre transplant or consolidation therapy is associated with significantly varying estimates of incidence and severity of BIPN, because of the variability of planned total dosages and the difficulty in extrapolating the final delivered cumulative BTZ dose from the reports. Moreover, results from a small (n=28) phase 2 trial showed that 21% of patients treated with lower dose BTZ schedules (1 mg/m^2) developed BIPN, whereas 15% of them presented clinically significant (grade 1/2) and 8% treatment emergent (grade 3/4) neurotoxicity (Jagannath et al. 2004).

The subcutaneous BTZ formulation and the reduced schedules of 1.3 mg/m^2 once a week instead of the classical twice-a-week regimen merit attention. A phase 3 trial tested the subcutaneous (sc) formulation, as an alternative to the traditional iv route, and the results, as outlined in table 1, suggested similar efficacy but, importantly enough, a lower incidence of neurotoxicity (Moreau et al. 2011a). Both arms were well balanced for the risk of developing peripheral neuropathy and the median cumulative dose as well as dose intensity were similar between arms (sc arm: 33.75 mg/m^2 and 5.13 mg/m^2 vs iv arm: 31.46 mg/m^2 and 4.89 mg/m^2). However, the results of this trial should be interpreted with caution because of some methodological issues, including the trial's endpoint, which was set to efficacy rather than safety and the 2:1 randomization, resulting in a smaller size of the iv arm. Another issue worth mentioning was that although the incidence of clinically significant BIPN (grade 1 and 2) was comparable between arms, there was evidence in this trial of significantly increased high grade (grade 3 and 4) neurotoxicity in patients allocated in the iv arm, compared to older results from large trials, which report a lower incidence of severe BIPN (Table 1).

Another phase 3 trial compared the efficacy of a chemotherapeutic regimen comprising BTZ-melphalan-prednisone plus thalidomide against the same schedule without thalidomide. In this trial, the protocol was amended after start, to evaluate whether dose reduction from twice-weekly to once-weekly BTZ infusions was able to maintain the efficacy and reduce toxicity (Palumbo et al. 2010). Despite differences in the planned dose, both groups received similar median cumulative BTZ doses (39.4 mg/m^2 vs 40.1 mg/m^2), because of a significant increase in both dose reductions and incidence of withdrawals in patients allocated to the twice-weekly group (n=134), compared to the once-weekly group (n=369). In any case, a significantly reduced overall incidence of grade 3/4 neurotoxicity was observed (8% vs 28%) in the once-weekly vs the twice-weekly group (Palumbo et al. 2010). However, it should be mentioned that although these findings appear interesting, they are not obtained from a pre-planned phase 3 trial and this issue might have induced bias.

Neuropathic pain ranks among the cardinal symptoms of BIPN and results from large trials show that the presence of severe neuropathic pain (grade 3-4) is reported by 5-16% of patients (San Miguel et al. 2008a; Palumbo et al. 2010; Hjorth et al. 2012; Mellqvist et al. 2013). Moreover, it is evidence that neuropathic pain of any severity develops more frequently in pre-treated patients with antineoplastic therapy (39% vs 15%), compared to those chemotherapy-naïve (Jagannath et al. 2005; Richardson et al. 2006a). Finally, BTZ therapy can also evoke autonomic dysfunction in 12-50% of patients, with constipation (12%) and orthostatic hypotension (50%) being the most frequent symptoms (Richardson et al. 2006b; Palumbo et al. 2010; Velasco et al. 2010; Mellqvist et al. 2013).

Risk factors of BIPN

Like almost any neurotoxic antineoplastic drug, the cumulative BTZ dose is the most significant risk factor for BIPN development. Neurotoxicity, in both pre-treated and newly diagnosed MM patients, usually appears within the first 5 cycles of treatment, being closely linked to the delivered cumulative dose. After the 5th cycle (at a cumulative dose of approximately 30 mg/m^2), its incidence slowly increases to reach a plateau at 42-45 mg/m^2, and does not increase thereafter (Richardson et al. 2009b, Dimopoulos et al. 2011).

However, the evidence of pre-existing neuropathy prior to the initiation of BTZ-based chemotherapy represents the strongest clinical risk factor for BIPN development (Lanzani et al. 2008; Dimopoulos et al. 2011). Advanced age was considered another significant risk factor for BIPN in some small series (Mateos et al. 2006; Corso et al. 2010). However, this association was not confirmed by the results of larger trials on the incidence or severity of neurotoxicity (Richardson et al. 2006b; Dimopoulos et al. 2011), thereby suggesting that elderly patients without any significant comorbidities are not more liable to develop BIPN and should be treated with the optimal BTZ dose. We also believe that advanced age per se is not a risk factor for CIPN and both its incidence and severity remain comparable between elderly and younger patients (Argyriou et al. 2006; Argyriou et al. 2013).

Other clinical factors, such as creatinine clearance (San Miguel et al. 2008b; Morabito et al. 2011), International Staging System Myeloma, excessive weight/obesity and diabetes have also not been identified as risk factors (Dimopoulos et al. 2011). Finally, it is suggested that BIPN might also be a proteosome inhibitor class effect, as up to 20% of patients may have sensory polyneuropathy prior to BTZ therapy initiation (Richardson et al, 2009a).

Clinical and electrophysiological characteristics of BIPN

There are no major updates in the clinical and electrophysiological spectrum of BIPN. It is widely acknowledged that patients usually complain of neuropathic pain, mainly located in the fingertips and toes, sensory loss to all modalities, distally attenuated, suppression or even abolishment of deep tendon reflexes in proportion to sensory loss and proprioception changes. Those cardinal symptoms and signs of BIPN are in line with a painful neuropathy due to dysfunction in all three major fibre (Aβ, Aδ, and C) types of sensory nerves (Argyriou et al. 2012).

From the electrophysiological point of view, nerve conduction studies usually reveal the typical findings of a toxic CIPN, consistent with distal, sensory, axonal neuronopathy. Findings of sensorimotor peripheral neuropathy can occasionally be seen (Park et al. 2013). Quantitative sensory testing confirms a persistent and severe impairment of Aβ, Aδ, and C fibres in BTZ-treated patients with chronic BIPN, due to loss of both epidermal nerve fibres and Meissner's corpuscles (Cata et al. 2007; Boyette-Davis et al. 2011).

Reversibility and long-term course of BIPN

The improvement or resolution of BIPN is normally observed in up to 85% of patients between 2 to 3.5 months after discontinuation of BTZ treatment (Richardson et al. 2005; Richardson et al. 2006b; Richardson et al. 2009a; Dimopoulos et al. 2011). Although the outcome appears similar between newly and pre-treated patients with other cytostatics, the neuropathy in this last group is resolved more slowly and neurotoxicity improves by at least one NCI-CTCAE grade within a median of 1.9 months in newly MM treated compared to 3.6 months in pre-treated patients (Dimopoulos et al. 2011). Compared to chemotherapy naïve, a much higher ratio

(36% vs 73%) of reduction or discontinuation of treatment is observed in those patients (Corso et al. 2010).

Finally, up to 30% of patients do not experience any recovery and neurotoxicity remains indefinitely in some cases (Richardson et al. 2006b; Dimopoulos et al. 2011; Argyriou et al. 2014) and, to our knowledge, the literature still contains no report of delayed de novo appearance of BIPN after BTZ therapy discontinuation.

Options for neuroprotection

To date, several agents, including various opioids, tricyclic antidepressants, anticonvulsants, serotonin-norepinephrine reuptake inhibitors, non-steroidal anti-inflammatory agents, vitamins and nutritional supplements, have been tested for their efficacy to symptomatically treat the neuropathic pain component in the context of BIPN (Argyriou et al. 2012). However, based on results from randomized controlled trials (RCTs), only duloxetine appears effective and well tolerated enough to alleviate BTZ-associated neuropathic pain.

A recently published RCT sought to determine the effect of a 5-week treatment with duloxetine, 60 mg daily, on average pain severity in chemotherapy-treated patients with various neurotoxic agents such as taxanes and platinum compounds. This study concluded that the use of duloxetine compared to placebo for 5 weeks resulted in a greater reduction in average pain (Smith et al.2013). It is acknowledged that no BTZ-treated patients were included in the latter trial, but in our opinion taking into account the major similarities amongst painful CIPN, duloxetine might also be effectively used against painful BIPN.

Similar to the case of symptomatic treatment, one cannot recommend based on RCTs the use of any neuroprotectants tested to date for prophylaxis from BIPN (Argyriou et al. 2014). Recently it was reported that the oral administration of lafutidine, a H2-blocker with gastroprotective activity, at a dose of 10 mg twice daily, might be able to prevent or improve neurotoxicity. In this small series of just 8 patients, it was shown that there was no BIPN after the first course, there were only grade 1 cases and there were no cases higher than grade 2, whereas none of the enrolled patients discontinued BTZ treatment because of BIPN (Tsukaguchi et al. 2013). However, considering the small sample size and other methodological limitations of that study, we cannot be sure about the significance of lafudine against BIPN, and larger, well-designed RCTs are needed before we can confidently conclude whether lafutidine is indeed useful for the amelioration of BIPN.

Table 2 outlines the available medications for the symptomatic treatment and/or prevention of BIPN. The choice of medication should be individualized taking into account the safety and tolerability of the prescribing drug as also potential drug interactions. In general, we advise to follow the "start low go slow" dogma, with initiation of pain relief therapy at small doses, slow up-titration to effective dose and then maintain for a period of 6-8 week. Opioids should be given with caution because of equivocal evidence regarding their efficacy in reducing the intensity of neuropathic pain, as also due to increased risk of adverse events and high addiction potential (McNicol et al. 2013).

In any case, and given the lack of robust evidence on the pharmacological management of BIPN, we still recommend adherence to the modification guidelines, as described and developed by previously published large trials, such as APEX (Richardson et al. 2009b). According to that scheme, a dose reduction to 1.0mg/m^2 is

required in case of grade 1 with pain or grade 2 (interfering with function but not with daily activities), withholding bortezomib treatment until BIPN resolves and then reinitiating at a dose of 0.7 mg/m^2 once weekly in case of grade 2 with pain or grade 3 (interfering with daily activities), whereas discontinuation of BTZ therapy is advised when sensorimotor neuropathy that significantly interferes with daily activities is evident. Moreover, the close neurological monitoring during BTZ treatment and eventual application of the above mentioned dose modification scheme in high risk patients has been demonstrated to be very useful in diminishing BIPN (Velasco et al. 2010; Cho et al, In press).

BIPN in the era of pharmacogenomics

So far, candidate gene approaches have been launched in order to develop a predictive genetic signature for the development of BIPN and several single nuclear polymorphisms (SNPs) in genes mainly involved in the BTZ pharmacokinetic and phamacodynamic properties have been shown relevant. For instance, a recently published study sought to report an extensive assessment of the gene expression profile of early-onset (within one treatment cycle) versus late-onset (after two or three treatment cycles) BIPN in BTZ-treated MM patients who were enrolled in the HOVON-65/GMMG-HD4 trial. In this study, it was found that the enzyme coding genes *RHOBTB2*, involved in drug-induced apoptosis; *CPT1C*, involved in mitochondrial dysfunction, and *SOX8*, involved in development of the peripheral nervous system have been found relevant to early-onset BIPN. Furthermore, two other SNPs in genes both involved in the development and function of the nervous system, i.e., *SOD2* and *MYO5A*, have been associated with late-onset BIPN. Finally, significant SNPs were noted in inflammatory genes *MBL2* and *PPARD*, and DNA

repair genes *ERCC4* and *ERCC3*. On the latter basis, authors claimed that specific genetic profiles might be associated with the risk of developing BIPN as also with its course and severity (Broyl et al. 2010).

In addition, after the genotyping of 2016 SNPs in 139 blood samples from BTZ-treated patients with MM, it was reported that genes associated with immune function (*CTLA4 rs4553808*, *CTSS rs12568757*), reflexive coupling within Schwann cells (*GJE1 rs11974610*), drug binding (*PSMB1 rs1474642*), and neuron function (*TCF4 rs1261134*, *DYNC1I1 rs916758*) have been associated with BIPN (Favis et al. 2011). Likewise, increased susceptibility to BIPN has been associated with SNPs in genes coding for steroid hormone biosynthesis, such as *CYP17A1 rs619824* (Corthals et al. 2011).

However, in our opinion, the available data need to be interpreted with caution because of several limitations in the available studies, including the implementation of post-hoc analysis of oncology-based databases of different, not pre-planned size and inappropriate outcome measures for neurological impairment. Another important issue concerns the lack of a pre-study hypothesis based on the known role of the investigated targets in the peripheral nervous system (Cavaletti et al. 2011). As such, further studies investigating SNPs in gene coding for neurologically-relevant targets in adequately powered, prospective cohorts of well-characterized BTZ-treated patients are warranted before a distinct predictive molecular profile for BIPN can be identified.

Conclusions

Peripheral neurotoxicity is a major and dose-limiting adverse event of BTZ-based chemotherapy. BIPN is generally characterized by evidence of symmetrical,

distally attenuated, neuropathic pain, paresthesias and dysesthesias. Depending on its severity and long-term course after the discontinuation of BTZ treatment, the impact on patient functionality and QOL might be detrimental. The incidence of BIPN mostly depends on BTZ dose and dose-intensity as well as upon the existence of risk factors, such as pre-treatment with neurotoxic agents or evidence of pre-existing neuropathy.

To date, there is no proper clinical predictor or biomarker to identify patients at high risk for development of treatment emergent and persistent BIPN. Pharmacogenetic approaches have been launched to this end, but the available clinically-relevant results from those studies remain fairly poor. Further studies implementing a proper methodological approach are needed.

Pharmacological interventions that would either prevent or ameliorate BIPN without altering the therapeutic benefits of BTZ are limited and rather ineffective. Thus, there is an obvious need for the development of new chemoprotective agents or further testing of already existing ones for their efficacy to prevent or limit BIPN. However, prior to clinical trials of these agents, it is important to be able to further elucidate the pathogenesis of BIPN as well as to assess it in a simple, valid, reliable and reproducible manner.

The comprehensive elucidation of the true spectra of BIPN pathogenesis and characteristics with the implementation of rational experimental, clinical, neurophysiological and pharmacogenetic approaches is expected to facilitate the identification of effective and safe early preventive and therapeutic interventions against BTZ-associated neurotoxicity.

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Table 1. Neuropathy incidence, clinical, and treatment schedules characteristics of phase 3 trials using BTZ adding the phase 2 (SUMMIT) trial that conducted the accelerated approval of BTZ by FDA.

Author	Size arm	Age (median)	Planned total dose (mg/m^2)	Median cycles (planned)	Neuropathy Grade	Comments
Multiple Myeloma						
Newly Diagnosed						
Palumbo (2010)	n=254	71y	67.3 (40.1*)	9[1]	G 3-4: 8%	Thalidomide containing regimens
	n=257	71y	67.3 (39.4*)		G 3-4: 5%	
San Miguel (2008)	n=344	71y	52	8 (9)	G 1: 14% G 2: 17% G 3-4: 13.3%	
Refractory or Relapsing						
Garderet (2012)	n=135	60y	62.4	7.5 (12)	G 1-2: 17.7% G 3-4: 23.3%	Thalidomide containing regimen
Hjorth (2012)	n=54	71y	5.2 per cycle until prog or tox	4	G 2: 18.8% G 3-4: 22.2%	30% dose reductions
Dimopoulos (2013)	n=317 n=320	61y 63y	5.2 per cycle until prog or tox	7 6	G 3-4: 7.6% G 3-4: 7.3%	
Moreau (2011)	n=148 sc	64.5y	41.6 (33.76*)	8 (8)	G 1-2: 32% G 3-4: 6% G 1-2: 37%	
	n=74	64.5y	41.6 (31.46*)	8 (8)	G 3-4: 16%	
Mikhael (2009)	n=638	62.7y	41.6	5 (8)	G 1-2: 19.1% G 3-4: 5.9%	5% discontinued
Orlowski (2007)	n=318	61y	41.6 (23.2*)	5 (8)	G 1-2: 9.7% G 3-4: 1.3%	
	n=318	62y	41.6 (24.4*)	5 (8)	G 1-2: 9.5% G 3-4: 2.8%	
Richardson (2005)	n=331	62y	57.2	29% completed 41.6 mg and 5% all cycles (11)	G 1-2: 28% G 3-4: 8%	
Richardson (2003)	n=202	60y	41.6	39% completed (8)	G 1-2: 19% G 3-4: 12%	Phase 2
Induction pre transplant and consolidation regimens						
Mellqvist (2013)	n=187	59y	41.6	5(6)	G 1-2: 52% G 3-4: 5%	

Sonneveld (2012)	n=221	57y	15.6[1]	47% completed (3[1])	G 1-2: 35 % G 3-4: 5%	Induction with vincristine containing agent
Rosiñol (2012)	n=129	57y	10.4	2 (2)	G 2: 15 % G 3-4: 9%	25% dose reductions and 2% discontinued
	n=130	56y	31.2	6 (6)	G 2: 46% G 3-4: 14%	
Cavo (2012)	n=160	57.4y	26	93% completed	G 2: 8.1% G 3-4: 8.1%	
Moreau (2011)	n=99 n=100	57y 58y	15.6 12	91% completed 95% completed	G 1-2: 59.6% G 3-4: 11.1% G 1-2: 50% G 3-4: 3%	4% discontinued Thalidomide containing regimen
Harousseau (2010)	n=121 n=119	57.2y 57.2y	15.6 15.6	100% completed	G 1: 21.3% G 2: 15.5% G 3-4: 7.1%	Vincristine and cisplatin containing regimens Toxicity not reported by separate treatment arms
Cavo (2010)	n=236	58y	26	94% completed	G 1: 18% G 2: 6% G 3-4: 10%	1% discontinuation
Follicular Lymphoma						
Coiffier (2011)	n=334	58y	32	5 (5)	G 1-2: 13% G 3-4: 3%	0.3% patients discontinued. BTZ dose 1.6mg/m^2

*Total administered dose of BTZ; Y: years; G: neuropathy grade by NCI-CTCAE; prog: progression; tox: toxicity; sc: subcutaneous; [1] Plus BTZ 1.3 mg/m^2 every 14 days during 2 years as maintenance. Every cycle usually contain four doses of BTZ 1.3 mg/m^2. Discontinuations and reduction doses reported are due to BIPN.

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Table 2. Medications for symptomatic relief and prevention against BIPN

Interventions against BIPN.	
Opioids	oxycodone, hydrocodone, morphine, fentanyl, tramadol
Tricyclic antidepressants	amytriptiline, nortriptiline, desipramine
Anticonvulsants	gapabentin, pregabalin
SNRIs	duloxetine, venlafaxine, bupropion
NSAIDs	celecoxib, rofecoxib, ibuprofen, acetaminophen
Vitamins	vitamin B6, vitamin C
H2 blockers	lafudine

SNRIs: serotonin-norepinephrine reuptake inhibitors; NSAIDs: non-steroidal anti-inflammatory drugs

Figure legend.

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)

Figure
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