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Peripheral neuropathy in patients with multiple myeloma: molecular effects of bortezomib

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Abstract

Multiple myeloma (MM) is a B cell neoplasm characterized by uncontrolled growth of malignant plasma cells within the bone marrow. The introduction of new treatment regimens and medicinal substances, particularly proteasome inhibitors (e.g. bortezomib or carfilzomib) and immunomodulatory drugs (e.g. lenalidomide, pomalidomide, and monoclonal antibodies), have radically changed MM therapy by improving the response rate and progression-free survival. However, these potentially effective drugs are associated with a number of side effects, the most serious of which include peripheral neuropathy, which appears in 40% of MM patients with bortezomib treatment and up to 70% with thalidomide treatment during long-term exposure. Usually, symptoms of neuropathy disappear after drug discontinuation or dose reduction. However, as a result, the effectiveness of the treatment is lowered and survival time is reduced. The pathogenesis of chemotherapy-induced peripheral neuropathy is not fully understood. Current research focuses on areas such as the change in the expression of genes responsible for the proper functioning of the nervous system, neuroprotective protein factors, oxidative stress, pro-inflammatory factors and epigenetic changes (miRNA, DNA methylation or histone acetylation). Thoroughly elucidating the mechanisms responsible for the development of chemotherapy-induced peripheral neuropathy will allow us to reduce/eliminate this side effect and improve quality of life for patients.

Key words: bortezomib-induced peripheral neuropathy, multiple myeloma

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Introduction

Multiple myeloma (MM) is a B cell neoplasm characterized by uncontrolled growth of malignant plasma cells within the bone marrow (BM). These cells are ordinarily able to produce monoclonal proteins. MM constitutes 1% of all neoplasms and 10% of all hematological malignancies [1]. The American Cancer Society estimates that 34,920 new cases of MM and 12,410 MM-related deaths will occur in 2021. MM is one of the most intractable malignancies and is characterized by the infiltration and growth of malignant plasma cells in the BM [2].

Despite the application of high-dose chemotherapy followed by autologous stem cell transplantation (SCT) and novel therapeutic agents, the prognosis for patients with MM is still unsatisfactory [3]. Specific genetic abnormalities are present in MM, including immunoglobulin heavy chain (*IGH*) translocations, RB1 deletion, 1q gain, hyperdiploidy or RAS gene mutations [4]. The first developmental step is the occurrence of recurrent chromosomal translocations involving the *IGH* locus at 14q32 [5]. The most frequent translocation is t(11;14)(q13;q32), which is observed in 15–20% of MM cases [6], followed by t(4;14)(p16;q32), with a 12–15% prevalence [7]. Other translocations, including t(14;16)(q32;q23), t(14;20)(q32;q11), and t(6;14)(p21;q32), are less frequently detected (<5%) [8]. The t(4;14)(p16;q32) translocation causes deregulation of histone methyltransferase

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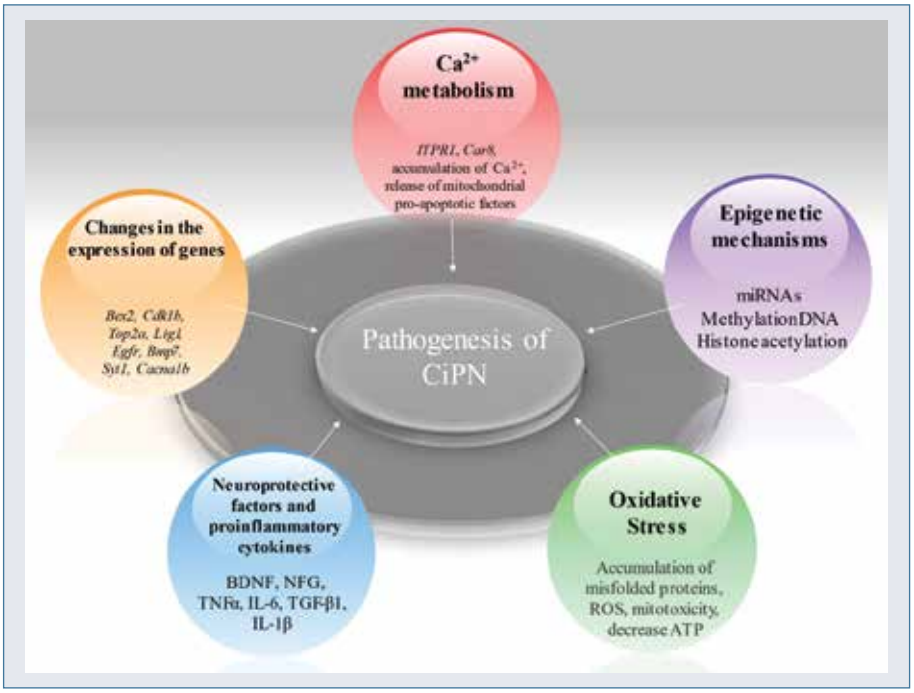

Figure 1. Pathogenesis of chemotherapy-induced peripheral neuropathy (CiPN); Ca^{2+} — calcium ions; BDNF — brain-derived neurotrophic factor; NFG — nerve growth factor; TNFα — tumor necrosis factor alpha; IL-6 — interleukin 6; TGF-β1 — transforming growth factor β1; IL-1β — interleukin 1β; ROS —reactive oxygen species; ATP — adenosine triphosphate

(MMSET), which promotes a decrease in H3K27me3 and H3K36me2 levels along the entire genome, and these changes cause the derangement of several genes, including cyclin D2 [9].

The second mechanism underlying the malignant transformation of plasma cells is hyperdiploidy, which is observed in approximately 55% of MM patients. For unknown reasons, odd-numbered chromosomes, such as 3, 5, 7, 9, 11, 15, 19 and 21 are increased in hyperdiploidy. The most prevalent hyperdiploidy (c.30%) is trisomy 11, which may cause cyclin D1 overexpression due to an increase in gene dosage [10]. The pathogenesis and survival time of patients is very heterogeneous. Introducing new treatment regimens and medicinal substances, particularly proteasome inhibitors [e.g. bortezomib (BTZ) or carfilzomib] and immunomodulatory drugs (e.g. lenalidomide and pomalidomide, and monoclonal antibodies), have radically changed MM therapy by improving the response rate and progression-free survival. State-of-the-art chimeric antigen receptor (CAR) T-cell immunotherapy uses mechanisms other than basic MM therapies. The CAR-T method involves the modification of patient or donor T cells to target specific cell surface antigens. The results of the latest clinical trials with anti-BCMA CAR-T lymphocytes have shown that patients with relapsed and/or refractory MM can achieve an objective response [11].

Unfortunately, similarly to the vast majority of drugs, those used in the treatment of MM also have a specific spectrum of side effects. One of the most important clinical problems seems to be chemotherapy-induced peripheral neuropathy (CiPN), which is mainly due to the symptom frequency, inconvenience for patients and dose-limiting effects [12]. CiPN occurs at varying severities during therapy, and its symptoms are observed in c.40% of MM patients with BTZ treatment [13] and up to 70% with long-term thalidomide treatment [14]. The incidence of CiPN depends on the dose, schedule and method of administration [15, 16].

Bortezomib-induced peripheral neuropathy (BiPN) is characterized by symmetrical distal sensory neuropathy with dominant pain symptoms. Subcutaneous administration of BTZ lowers neuropathy (38% vs. 53%) compared to former intravenous administration [17].

The degree of neuropathy is determined according to various scales. However, the most common scale is the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) [18]. This scale includes three types of neuropathy: a) sensory, b) autonomic-sensory, and c) sensorimotor. Moreover, in each type of neuropathy, its degree can be determined depending on the severity of symptoms (where 0 means no symptoms and 4 means permanent functional impairment) [19].

To elucidate the pathogenesis of CiPN, global research has focused on several areas, as shown in Figure 1.

This review focuses on the pathophysiology of CiPN based on the latest scientific data and our own research.

Pathophysiology of BiPN

Bortezomib is a boron-containing organic compound that specifically and reversibly inhibits the chymotrypsin-like activity of the 26S proteasome. Inhibition of proteasome activity by BTZ disrupts the processes necessary for proper functioning, which consequently leads to cell death [20]. The mechanism of action of BZT is disruption of the cell cycle, induction of apoptosis, disturbance of bone marrow microenvironment, and inhibition of nuclear factor kappa B (NFκB) [21].

One of the first studies on the mechanisms of bortezomib-induced neurotoxicity was conducted by Cavaletti et al. in 2007 [22] using a rat model. Studies have shown that BTZ causes disturbances in satellite cells and Schwann cells of the sensory nerves. Meregalli et al. [23] proved that the drug also affects synapses and causes unmyelinated C-fiber axonopathy. BTZ cytotoxicity is also attributed to disturbances in cellular calcium homeostasis as a consequence of abnormal mitochondrial function [24]. The accumulation of Ca^{2+} ions in mitochondria causes rupture of the outer membrane and then the release of mitochondrial proapoptotic factors into the cytosol [25, 26]. In addition, the downregulation of genes responsible for calcium metabolism, such as ITPR1 and Car8, may have a significant impact on the functioning of the nervous system, including the excitability of neurons, the growth of neurites and the release of neurotransmitters [27]. Protein neuroprotective factors, especially neurotrophins (NTs), play a special role in the context of nerve cell homeostasis. The family of classic neurotrophins includes nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin 3 (NT-3) and neurotrophin 4/neurotrophin 5 (NT-4/5). These proteins are synthesized and released mainly by nerve cells [28, 29] but also by muscle [30], endothelium [31, 32], spleen, adipose tissue, liver, lung and hematopoietic cells [33–35]. Neurotrophins influence the proliferation, differentiation, viability and death of neuronal and non-neuronal cells. Due to the significant influence of NTs on the nervous system, lowering their concentration in tissue may contribute to the development of neuropathy [36, 37]. This hypothesis seems to be confirmed by Azoulay et al. [38], who described decreased BDNF concentrations in the plasma of patients with MM and symptoms of BiPN relative to patients treated with the same regimen but without symptoms of BiPN.

Peripheral neuropathy is associated with an increase in reactive oxygen species and a decrease in endogenous antioxidants [39]. BTZ inhibits the actions of the proteasome, which causes the accumulation of misfolded proteins that would be degraded under physiological conditions. Consequently, subsequent protein folding attempts generate high levels of reactive oxygen species (ROS) [40]. Thus, the development of BiPN may be related to mitotoxicity in primary axons (PNSAs) resulting from reduced mitochondrial bioenergetics. This association is confirmed by the fact that the development of mechano-hypersensitivity induced by BTZ is prevented by the administration of MnTE-2-PyP(5+), which belongs to the group of peroxynitrite decomposition catalysts (PNDCs, i.e. compounds with redox activity that detoxify peroxynitrite by catalyzing its isomerization or reduction to nitrates or nitrites). In addition, the action of BTZ is related to the nitration and inactivation of superoxide dismutase in the mitochondria and a meaningful decrease in adenosine triphosphate (ATP) production [41].

BTZ also causes higher proteotoxic stress associated with increased expression of heat shock proteins, reduced membrane potential of mitochondria, and ubiquitination of protein K48. Furthermore, BTZ downregulates the content of mitochondrial oxidative phosphorylation complexes, thereby decoupling protein 2 (UCP2) and voltage-dependent anion channel 1 (VDAC1) [42].

Proinflammatory cytokines are another area of research that may bring us closer to solving the problem of the pathomechanism of BiPN [43]. One of the most extensively studied proinflammatory factors is tumor necrosis factor alpha (TNFα). Zhao et al. [44] showed that during the administration of BTZ to rats, the expression of TNFα was significantly increased. Another study confirmed that the expression of TNFα was upregulated in the dorsal root ganglia after treatment with BTZ in a mouse model [45]. Furthermore, the same study showed increased expression of other proinflammatory cytokines, such as interleukin (IL) 6, transforming growth factor β1 (TGF-β1) and IL-1β, in the dorsal root ganglia, which was directly related to the administration of BTZ [45].

An increasing number of reports have focused the influence of BTZ on gene expression and epigenetic mechanisms. Although BTZ contributes to the inhibition of tumor progression, it also causes disturbances in cells that lead to the development of BiPN and other side effects such as thrombocytopenia, neutropenia or anemia. The activity profile of BTZ includes damage to DNA strands and inhibition of repair and replication processes and the cell cycle [46].

Epigenetics describes inherited gene expression mechanisms that are not dependent on changes in DNA sequences and provide diversity in the functioning of cells based on identical genetic materials. Epigenetic mechanisms include histone modification, DNA methylation, miRNA-based gene regulation, and monoallelic gene expression (parental imprinting, inactivation of the X chromosome) [47]. Fernández de Larrea et al. [48] demonstrated a relationship between the degree of total DNA methylation and the survival time of patients with relapsed MM who received treatment regimens based on BTZ. Patients with total DNA methylation >3.95% achieved longer overall survival (OS). In addition, patients with a relatively low percentage of methylation (<1.07%) of the *NFKB1* gene also showed a longer overall survival after BTZ therapy [48]. Epigenetic mechanisms

include the regulation of gene expression with small single-stranded noncoding microRNAs (miRNAs). During BTZ therapy, a decreased level of Let-7f has been observed, which promotes vascular neoplastic processes by lowering the expression of genes responsible for antiangiogenic effects [49]. Administering anti-Let-7f enhances apoptosis and reduces the proliferation rate of established MM cell lines [50].

Moreover, BTZ induces changes in the expression of miRNA molecules whose genes are involved in inhibiting the development of cancer cells or in the functioning of the nervous system. For example, miRNA-181, miRNA-20a, miR-342-3p, miR-128, miR-17-92 and miR-29b regulate genes involved in the process of neurogenesis and neuronal differentiation, and their plasma concentration is significantly lowered during BTZ therapy while the level of miRNA-34a is then elevated, which results in inhibition of BDNF expression and activation of the neuronal apoptosis process [51].

Currently, our research group is focused on gene expression and epigenetic changes that may influence the development of BiPN, which has not been well explored. We have shown changes at the molecular level that may contribute to inhibiting the development of both cancer [52] and neuropathy [53]. Two representative established cell lines, a) SH-SY5Y neuroblastoma and b) a PC12-derived nerve cell line, were used in these studies. Cells were treated with BTZ (50 nM/L) for 24 h, and global gene expression and miRNA expression were analyzed using genome-wide RNA and miRNA microarray technologies. Studies have shown that BTZ might exert toxic effects on both neuroblastoma cancer and PC12 nerve cells and regulate miRNA/mRNA interactions that affect important cellular functions. BTZ has been shown to exert a meaningful inhibitory effect on the proliferation (*TFAP2B*, *PEG10*) and apoptosis (*HSPA1B*, *CLU, HMOX1*) of human neuroblastoma cells. These mechanisms could be responsible for the advantages of using BTZ for cancer treatment. In contrast, in nerve cells, BTZ primarily inhibits the cell cycle (*Bex2, Cdk1b, Lin9*), DNA repair processes (*Top2a, TopBP1, Lig1*, *Ercc6*), neuronal morphogenesis (*Egfr, Bmp7, Ilk*), and neurotransmitter secretion (*Syt1, Cacna1b, Lin7a*). The obtained outcomes show differences in the major metabolic pathways and biological processes that are disturbed as a result of the action of BTZ in cancer and nerve cells.

An important observation from the conducted research was the mRNA/miRNA relationship. The most interesting correlation between miRNA and target genes in neuronal cells differentiated from PC12 cells was the decreased levels of miR-130a-3p and miR-152-3p, which resulted in an increase in *Gadd45* gene expression. This gene belongs to a group of genes whose expression at the transcript level is enhanced under stress conditions of growth arrest and exposure to DNA damaging agents, such as drugs or mutagens. In contrast, cancer cells showed changes in the correlation between mRNA and target genes, which influenced various processes such as a) promoting apoptosis (↓ hsa-miR-330-3p — ↑ *MDM2*; ↓ hsa-miR-124-3p — ↑ *SNAI2*; ↓ hsa-miR-503-5p — ↑ *DYNLL2*), b) regulating neurogenesis (↑ hsa-miR-21-3p — ↓ *NCAM2*; ↑ hsa-miR-335-5p — ↓ *SOX4*; ↑ hsa-miR-34a-5p — ↓ *CDK6*), and c) activating processes of neuronal death (↓ hsa-miR-6880-5p — ↑ *C12orf5*; ↓ hsa-miR-26b-5p — ↑ *DDIT4*; ↓ hsa-miR-26b-5p — ↑ *HSPD1*) (↑ miRNA/target gene expression; ↓ miRNA/target gene expression).

In subsequent studies, we revealed a significant effect of the immune response in myeloma patients on the development of CiPN. We observed increases in the levels of proinflammatory cytokines (CCL2, IL-1β, IFN gamma, properdin) and complement proteins (complement 9, factor D) at both the transcript and protein levels. In addition to understanding the pathogenesis of BiPN, an important goal is identifying biomarkers for faster diagnosis of neuropathy. Our recent studies have identified miR-22-5p as a potential marker of CiPN in patients with MM.

Resistance to bortezomib in multiple myeloma

Resistance to BTZ development in MM patients is a serious therapeutic problem. Current scientific reports show the involvement of PSMB5 mutations and proteasome subunit upregulation, changes in protein and gene expression in response to cell survival, stress, and antiapoptotic pathways in the development of resistance to BTZ [54, 55]. The epigenetic changes triggered by BTZ may contribute to the development of resistance. Class I histone deacetylases (HDACs) determine the sensitivity of proteasome inhibitors, and histone methyltransferase (EZH2) alters the transcription of antiapoptotic genes during the acquisition of cell adhesion-mediated drug resistance (CAM-DR) by myeloma cells. In addition, histone methyltransferase (MMSET) has been shown to confer drug resistance to myeloma cells, thereby facilitating DNA repair [56].

Additional research by our group in this area focused on analyzing the methylation profile following exposure of neuroblastoma cells to BTZ. The study consisted of treating neuroblastoma cells with BTZ for 24 hours and then leaving them for 12 days (in medium without BTZ) to examine the methylation profile in the daughter cells and assess the extent of proliferation after subsequent doses of BTZ. The obtained results showed that BTZ induced marked genome-wide methylation changes in cells. The obtained results showed a significantly altered global methylation profile after treatment of the cells with BTZ, manifested by hypermethylation of genes which were hypomethylated in control cells and a decrease in the

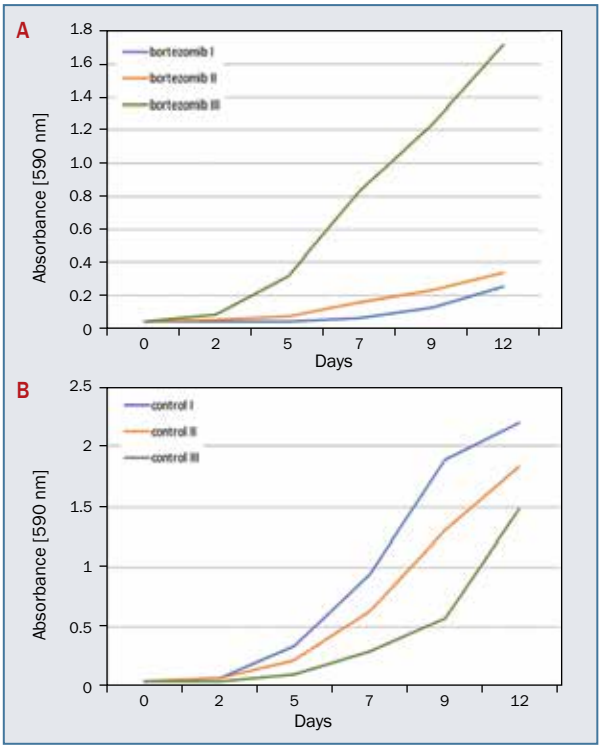

Figure 2A, B. MTT test results showing induction of unusual cell proliferation potential that increased with subsequent treatments

degree of methylation in hypermethylated genes. The observed changes mainly concerned the pathology of cancer pathways.

The consequence of these changes may be to bypass the primary antitumor activity of BTZ and develop a treatment-resistant phenotype. To investigate the acquisition of a proliferative phenotype, cells that had recovered after the first round of BTZ treatment were treated three times. Repeated treatment led to the induction of an unusual cell proliferation potential that increased with subsequent treatments (Figure 2) [57].

Conclusion

The pathogenesis of BiPN is still extremely unclear, and its development involves many molecular mechanisms; therefore. A relatively new area of research in this field is focused on the epigenetic mechanisms that may constitute the basis for the development of PN due to the global regulation of gene expression in many processes. Thorough elucidation of the mechanisms responsible for the development of BiPN will allow us to reduce/eliminate this side effect and improve the quality of life of patients.

Author's contributions

KŁ wrote a draft of the manuscript and prepared the figures, BM reviewed and edited the manuscript.

Conflict of interest

The author declares no conflict of interest.

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Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; Uniform requirements for manuscripts submitted to biomedical journals.

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