BORTEZOMIB-BASED CHEMOTHERAPY INDUCED NEUROTOXICITY: FOCUS ON CYTOSKELETAL AND MITOCHONDRIAL DYSFUNCTION

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The proteasomal system is involved in the turnover of damaged proteins and it is responsible for their degradation. Because of its role in oncogenesis, the inhibition of the proteasome system is a promising therapeutic target for neoplastic treatment. The accumulation and deleterious effects of toxic proteins are frequently induced by exposure to chemotherapeutic drugs and 20S proteasome inhibitors, such as bortezomib (BTZ) and carfilzomib (CFZ) have been approved by the U.S. Food and Drug Administration (FDA) for the treatment of multiple myeloma (MM) and some other liquid tumours. Although the survival of MM patients has been improved by the introduction of both drugs-based therapies, these proteasome inhibitors have several limitations, including chemotherapy-induced peripheral neurotoxicity (CIPN). Since it is becoming increasingly clear that cytoskeletal integrity and mitochondrial function are intricately linked, we compared these targets after BTZ and CFZ treatments *in vitro*. Primary culture of dorsal root ganglion (DRG) sensory neurons isolated from adult mice were treated with BTZ 10 nM and CFZ 60 nM for 24 hours, and measurement of energy metabolism were investigated using XFe24 Seahorse Analyzer, while a morphological analysis of mitochondria was performed *in silico* using the toolset MiNA (Mitochondrial Network Analysis). Moreover, by immunoblotting we have evaluated drug-induced alterations of proteins involved in cytoskeleton, mitochondrial oxidative phosphorylation, and molecular motors transport.

BTZ was shown to induce several cytoskeletal damage in terms of increased levels of delta2-tubulin, acetylated tubulin and MAP2 expressions compared to both CFZ-treated cells and untreated cells. Conversely, the evaluation of the bioenergetic mitochondrial metabolism revealed a reduction in basal and maximal respiration for both chemotherapeutic drugs. Similarly, both BTZ-and CFZ cultures showed a decrease in ATP production compared with the untreated cells. These alterations were associated with a disruption in the organization of the mitochondrial network. These findings suggest that BTZ-induced neurotoxicity mechanism is correlated

with peculiar cytoskeletal alterations, while changes in mitochondrial skeleton morphology along with reduced mitochondrial respiration may be a common mechanism underlying cell toxicity. Understanding these pathways may provide specific therapeutic targets for the treatment of BTZ-induced CIPN.

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