BORTEZOMIB-INDUCED PERIPHERAL NEUROPATHY: STUDY OF PROTEASOME INHIBITION AND MICROTUBULE STABILIZATION MECHANISMS IN RAT MODEL

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Bortezomib is an antineoplastic agents that is often used to treat the multiple myeloma and of some lymphomas. Although its well-known antitumor activity, its effectiveness is limited by the highly incidental development of severe peripheral neuropathy (BIPN). This neuropathy is characterized by dysesthesia, numbness and a painful sensations. In order to obtain a pre-clinical model to improve our understanding of BIPN molecular pathways, we performed an rat model in which bortezomib (0,20 mg/kg) was administered three times weekly for eight weeks, followed by a four-week follow up period.

At the end of the treatment period, we assessed nerve conduction velocity (NCV) and pathological changes in caudal nerve, dorsal root ganglia (DRGs), and sciatic nerve. Afterwards, we verified the involvement of proteasome inhibition and also we evaluated the microtubule stability in sciatic nerve by comparing the distribution of acetylated tubulin between polymerized (P) and soluble (S) fractions by western blot experiments.

The neurophysiological evaluation demonstrated a reduction in NCV both at eight weeks and after the follow up period: at the pathologic analysis, caudal nerves were the most affected structures, whereas DRGs showed a vacuolization in the cytoplasm in sensory neurons and of satellite cells, although the sciatic nerves evidenced a mild axonopathy. Proteasome activity assay was performed on peripheral blood mononuclear cells (PBMCs), sciatic nerve and brain: PBMCs and sciatic nerve recovered quickly in the acute setting, while maintaining strong inhibition until 48 hours after last injection when the drug was chronically administered. Moreover, at six and eight weeks of treatment, we observed the increase of acetylated alpha-tubulin in the polymerized fraction in sciatic nerves of BTZ-treated animals as compared with control, that returning at baseline during follow up period.

In conclusion, our results demonstrated that BTZ is able to induce a toxic effect on peripheral nervous system by the inhibition of proteasome and the stabilization of microtubule. Consequently, to deepen the study on these two possible neurotoxic mechanisms that underlying BIPN, will be important for developing neuroprotective drugs.

NEUROPATIA PERIFERICA INDOTTA DA BORTEZOMIB: STUDIO DEI MECCANISMI DI INIBIZIONE DEL PROTEASOMA E DI STABILIZZAZIONE DEI MICROTUBULI IN UN MODELLO DI RATTO