BORTEZOMIB-INDUCED PERIPHERAL NEUROPATHY: STUDY OF DIFFERENT MOLECULAR MECHANISMS

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Bortezomib (BTZ) is a chemotherapy drug that shows a high antineoplastic activity against multiple myeloma and some type of solid tumours. This drug acts by inhibiting protein degradation by the proteasome; however its clinical use is limited by the onset of a severe peripheral neuropathy associated with neuropathic pain. Different mechanisms may underlie the development of peripheral neuropathy among which the proteasome inhibition and the alteration of microtubule's stability. To study these mechanisms we used a well-characterized rat model of BTZ-induced peripheral neuropathy in which BTZ was administered in Wistar rats at the dose of 0.20 mg/kg three times/week for 8 weeks.

To confirm the onset of peripheral neuropathy we performed neurophysiological measures of the caudal nerve conduction velocity and the morphological analysis at the light microscope of the sciatic nerve and the dorsal root ganglia.

After one single dose of BTZ and at the end of the 8 weeks-period of treatment, the level of proteasome inhibition was evaluated by the proteasome activity assay in blood mononuclear cells, sciatic nerve and brain by fluorimetric assay. Furthermore, the alteration of microtubule's stability was examined in sciatic nerve by comparing the distribution of acetylated alpha-tubulin between polymerized and soluble fractions by western blot experiments.

When BTZ was injected in a single acute dose we observed the recovery of the proteasome activity within 24 hours from the drug administration while when the drug was chronically administered, the proteasome activity remained suppressed. These different results were probably due to a cumulative effect of chronic administration of BTZ. Moreover, at the end of the treatment we observed the increase of acetylated alpha-tubulin in the polymerized fraction in sciatic nerves of treated animals as compared with control.

This study suggests a potential explanation for the development of peripheral neuropathy induced by chronic administration of BTZ, through the ability to induce a proteasome inhibition and to suppress the cytoskeleton dynamics.

In conclusion, this model showed that BTZ is able to induce a toxic effect on peripheral nervous system by the inhibition of proteasome and the stabilization of microtubule. Moreover this model can be useful for the study of "*de novo*" proteasome synthesis and the recovery of its activity and to characterize the potential role of microtubule stabilization in the BTZ-induced neurotoxicity.

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