EFFECT OF PROTEASOME INHIBITION ON THE CENTRAL AND PERIPHERAL NERVOUS SYSTEM

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AIM Bortezomib (VELCADE®) is the first proteasome inhibitor entered into clinical evaluation as antineoplastic agent. Despite clear evidence of effectiveness, bortezomib use is still limited and one of the reasons is bortezomib-induced severe peripheral neuropathy. In the present study we report the first animal model of bortezomib-induced peripheral neuropathy, investigated with neurophysiological and pathological methods. The aim of this study is to characterize for the first time the effect of bortezomib administration on the central and peripheral nervous system
MATERIAL AND METHODS Female Wistar rats received bortezomib twice (2q7d) or three times (3q7d) weekly for a total of 4 weeks at the dose of 0.20 mg/kg/day (i.e. 1.2 and 1.8 mg/m^2). At baseline, on days 14, 21 and 28 each animal underwent the determination of sensory nerve conduction velocity (SNCV). At the end of treatment rats were sacrificed and dorsal root ganglia (DRG) and sciatic nerves were obtained for light and electron microscope examination.
RESULTS Bortezomib induced a significant reduction in SNCV. In the rats treated with the 2q7d schedules, the effect of bortezomib administration on SNCV was less evident than in the 3q7d. At the pathological level satellite cell changes were frequently observed in the DRG, while neurons were generally of normal aspect. Endoplasmic reticulum and, less frequently, mitochondia were the most obvious intracellular targets of the toxicity. In the sciatic nerve both axonal and myelin changes were evident. Spinal cord was of normal aspect at the light and ultrastructural examination
CONCLUSIONS Our animal study, which is relevant to human bortezomib neuropathy, reports for the first time that neurophysiological and pathological changes induced by the chronic administration of bortezomib on the peripheral nervous system in a rat model increased with dose and frequency of administration. Moreover, it indicates that using our experimental paradigm the central nervous system is not affect by bortezomib administration.