CHARACTERIZATION OF BORTEZOMIB- INDUCED PERIPHERAL NEUROPATHY IN EXPERIMENTAL ANIMAL MODELS

Meregalli Cristina, Canta Annalisa, Carozzi Valentina, Oggioni Norberto, Marmiroli Paola, Tredici Giovanni.

Department of Neuroscience and Biomedical Technologies, University of Milan Bicocca, Monza

The anticancer drug bortezomib (BTZ) is a reversible 20S proteasome inhibitor used in the treatment of multiple myeloma and certain lymphomas.
BTZ-induced peripheral neuropathy (BIPN) is a widely recognised dose-limiting side effect of this drug that can influence the patient's quality of life. Few data are available about the mechanisms underlying BTZ neurotoxicity.
In this work we used different animal models to investigate the BTZ-induced peripheral nervous system (PNS) impairment. In a preliminary study we used Wistar rats treated with BTZ 0.20 mg/kg 3qwX4. In order to mimic the clinical long-term use of BTZ, and to reproduce the typical pain symptoms in BTZ-treated patients, we designed a second experimental model in which we extended the treatment phase up to 8 weeks, preserving the drug dose. In both rat models we demonstrated an axonopathy, but only through the second ones we assessed the severity and the time-course of BTZ-induced neuropathic pain. We then set up a third study in order to evaluate the neurotoxicity and the antitumor activity of BTZ in the same *in vivo* model. Since only few cancer cell lines are able to induce the development of cancer in immunocompetent rats, we decided to use Balb/c (immunocompetent) and Hsd Athymic nude nu/nu (immunodeficient) murine models of chronic BIPN. BTZ was admistered 0.4 or 0.8 mg/kg, for 4 or 6 weeks. In both models we investigated the sensory/motor and sensory nerve conduction velocity (NCV) in the caudal and digital nerves. In all models BTZ decreased the NCV, indicating a neurophysiological impairment; this damage was confirmed by morphological alterations in the PNS.
These results suggest that all the models mentioned above are usefull to reproduce the BIPN. Furthemore, mice model will allow us to study the neurotoxicity induced by BTZ and its activity against cancer of human and murine origin in the same *in vivo* model.

Supported in part by a research grant from the "Fondazione Banca del Monte di Lombardia"