NEUROTOXICITY INDUCED BY CISPLATIN, TAXOL AND BORTEZOMIB IN IMMUNOCOMPETENT CD1 MICE AND IMMUNODEFICIENT NUDE MICE

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Chemotherapy-induced peripheral neuropathy (CIPN) is a major dose limiting side effect of commonly used chemotherapeutic agents, including cisplatin (CDDP), paclitaxel (PT), and bortezomib (BZ). Several rat models of CIPN had been established in the past to describe the mechanisms of its development. Since only few cancer cell lines are able to induce the development of cancer in the rat, we decided to reproduce into two different murine models the neuropathic condition to allow the study of the neurotoxicity and the antitumor activity of the antineoplastic drugs against cancers of both murine and human origin.
In this study, in order to characterized the neuropathological impairments induced by chemotherapy treatment in CD1 (immunocompetent) and Hsd Athymic nude (immunodeficient) mice, CDDP (4 mg/kg, i.p, 2qw), or PT (80 mg/kgi.v, 1qw) or BZ (0.8 mg/kg, i.v, 2qw) were administered for a 4 and 6 weeks-period. The neurotoxicity was evaluated by sensory/motor and sensory nerve conduction velocity (NCVs) in the caudal and digital nerves, respectively. Sciatic nerve and dorsal root ganglia (DRG) specimens, were processed for microscope analysis to evaluated the presence of any pathological alteration.
In both CD1 and nu/nu models of chronic CIPN, we observed that PT and CDDP induced significant alterations in body weight after 4 and 6 weeks of treatment. In the CD1 model, electrophysiological evaluation at the 4 or 6 weeks evidenced a significant reduction in both caudal and digital NCV induced by all compounds, while the nu/nu model revealed a significant difference of these parameters only at the 6 weeks. These functional damages were confirmed in both murine models by the morphological analysis: axonal degeneration was present in the sciatic nerves of animals treated with PT and BZ while alterations in the DRG were evident in CDDP and BZ-treated ones. At the same drugs concentrations, less severe functional damages were observed in Hsd nude mice compared to CD1 mice.
In conclusion both murine models showed a toxic effect on peripheral nervous system induced by all drugs mentioned above. Therefore, these models can be useful for the study on the neurotoxicity related to the treatment with CDDP, PT and BZ and antitumor activity against cancer of human and murine origin.

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