

PERIPHERAL NEUROPATHY INDUCED BY CHRONIC ADMINISTRATION OF CISPLATIN, TAXOL AND BORTEZOMIB IN SEVERAL MURINE MODELS

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Cisplatin (CDDP), Taxol (TAX) and Bortezomib (BZ) are chemotherapeutic drugs commonly employed in clinical practice for the treatment of solid and haematological tumors. Their clinical use is limited by the development of a peripheral neuropathy characterized by sensory alterations, pain and, in part, by motor and autonomic dysfunctions.

Several rat models had been performed to study and describe the mechanisms of the peripheral neurotoxicity induced by these drugs. However, since only few cancer cell lines are able to induce the development of cancer in the rat, we focused our attention on mice models to allow the combined study of the antineoplastic activity and of the neurotoxic effects of the anticancer compounds. Moreover, different mice strains should be useful for different kind of studies.

Here we investigated the interactions between the mice genotype and their drug response to determine the susceptibility to the development of chemotherapy-induced peripheral neuropathy. To this aim, we investigated the neurophysiological and neuropathological alterations induced by the chronic treatment with different chemotherapy drugs in female Balb/c, CD1 and c57 mice and in male c57 and FVB mice.

Mice were injected with Cisplatin (2, 4 mg/Kg, ip, 2qw), or Taxol (50, 70, 80 mg/Kg, iv, 1qw) or Bortezomib (0.4, 0.8 mg/Kg, iv, 2qw) for a period of 4-6 weeks. At the end of the treatment the nerve conduction velocities (NCVs) were determined in the caudal and in the digital nerves and the dorsal root ganglia (DRG) and sciatic nerves collected for the neuropathological analysis; behavioural tests were performed to study if these drugs are able to induce allodynia or hyperalgesia.

In all mice models we observed that TAX and CDDP induced a significant alteration in body weight at the end of the treatment. All the drugs induced a significant reduction in the caudal and digital NCV in Balb/c and CD1 mice. TAX and BZ caused the axonal degeneration of the sciatic nerves while CDDP and BZ morphological alterations in the DRG. In c57 female mice, only BZ induced a significant reduction in caudal NCV while in c57 male mice only CDDP caused neurophysiological impairments. By contrast, male FVB mice showed any neurophysiological alterations. All these models, except FVB mice, have shown the onset of allodynia and hyperalgesia at the end of the treatment.

In conclusion we can affirm that, even if at different extent, Balb/c, CD1 and c57 mice were able to develop the different chemotherapy-induced peripheral neuropathies. Moreover, also the gender seemed to be involved in the severity of the neuropathy. By contrast, FVB mice were less susceptible to the neurotoxic damage.

This study would give a useful guideline for the choice of mouse strains in the combined studies of the antineoplastic activity and of the neurotoxic effects of chemotherapy drugs.

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