

CHARACTERIZATION OF NEW MURINE MODELS OF PERIPHERAL NEUROPATHY INDUCED BY CHRONIC ADMINISTRATION OF ANTINEOPLASTIC DRUGS.

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Cisplatin, oxaliplatin, paclitaxel, epothilone-B and bortezomib represent some of the most employed treatments in colon, genitourinary cancers and multiple myeloma. Nevertheless, their clinical use is often associated to the development of a peripheral neuropathy characterized by sensory alterations, pain and, in part, by motor and autonomic dysfunctions.

Several rat models of chemotherapy-induced peripheral neuropathy (CIPN) had been established in the past to describe the mechanisms of its development and pathogenesis revealing that all chronic chemotherapy regimens cause neurophysiological impairments and alterations in peripheral nerves and DRG. However, since only few cancer cell lines induce the development of cancer in the rat, this model doesn't represent the most effective way to study, at the same time, the antineoplastic activity and the neurotoxic effects of the anticancer compounds.

Here we report a neurophysiological and neuropathological characterization of new immunocompetent (IC) and immunodeficient (ID) murine models of chronic CIPN.

Balb-c (IC) and Hsd Athymic nude nu/nu (ID) mice were treated with cisplatin (2, 4 mg/Kg), or paclitaxel (50, 70, 80 mg/Kg) or oxaliplatin (3.5 mg/Kg), or epothilone-B (2, 4 mg/Kg), or bortezomib (0.4, 0.8 mg/Kg), for a 4-6 week-period. Sensory/motor and sensory nerve conduction velocities (NCVs) were determined in the caudal and the digital nerves. DRG and sciatic nerves were collected for neuropathological and morphometrical analysis. The electrophysiological studies revealed that in Balb-c mice all compounds determined a significant reduction in caudal NCV, and at a lesser extent, in the digital NCV. These functional damages were confirmed by morphological observations describing an axonal degeneration in the sciatic nerves induced by paclitaxel, epothilone-B and bortezomib and alterations in DRG induced by platinum compounds and bortezomib. Platinum compounds determined also a quantitative reduction- in- size of DRG sensory neurons. At the same drugs concentrations, significantly less severe functional and morphological damages were observed in Hsd nu/nu peripheral nervous system suggesting a possible role of the B cell-mediated immunity in the severity of the CIPN. Higher concentrations of the antineoplastic drugs or different schedules of treatment were needed to induce similar functional and morphological alterations in DRG and peripheral nerves to those observed in Balb-c mice.

These results suggest that the selected treatment schedules were able to induce both sensory/motor and sensory peripheral neuropathies in the IC and ID mice and allow to combine the study of peripheral neurotoxicity of chemotherapy drugs to their anti-tumour activity against cancers of both murine and human origin.

Partially supported by an unrestricted research grant from "Fondazione Banca del Monte di Lombardia".