TITLE:

Characterization of new murine models of peripheral neuropathy induced by chronic administration of antineoplastic drugs.

SHORT TITLE:

Mice models of toxic peripheral neuropathy

AUTHORS:

Carozzi V.*, Canta A, Oggioni N., Sala B., Meregalli C., Chiorazzi A., Bossi M., Cavaletti G.

Department of Neurosciences and Biomedical Technologies, University of Milano-Bicocca, Monza (MI), Italy.

***PRESENTER, ABSTRACT SPONSOR**

- AACR MEMBER NUMBER (ASSOCIATE): ……

-e-mail: v.carozzi@campus.unimib.it

-Tel: 00390264488122; Fax: 00390264488253

MAIN BODY:

In this study we report the neurophysiological and neuropathological characterization of new murine models of chemotherapy-induced peripheral neuropathy (CIPN).

Cisplatin, oxaliplatin, paclitaxel, epothilone-B and bortezomib represent some of the most frequently employed chemotherapy treatments in breast cancer, colon cancer, genitourinary cancers and multiple myeloma. Nevertheless, the clinical use of these drugs is often associated to the development of a potentially severe peripheral neuropathy characterized by sensory distal alterations such as pareshesias and dysesthesias, ataxia, burning sensations, diminished reflexes and, at least in part, by motor and autonomic dysfunctions.

Several rat models of CIPN had been established in the past to describe the mechanisms of its development and pathogenesis revealing that, as well as in humans, all chronic chemotherapy regimens cause neurophysiological impairments, neuropathological and molecular alterations in

peripheral nerves and DRG. However, since only a limited number of cancer cell lines is able to induce the development of cancer in the rat, this animal model does not represent the most effective way to study, at the same time, the antineoplastic activity and the neurotoxic effects of the anticancer compounds.

In this work, in order to characterize the neurophysiological impairments induced by chronic chemotherapy treatment in balb-c mice, the drugs were administered for a 4 weeks-period. Cisplatin at the doses of 2 or 4 mg/Kg, paclitaxel 50 or 70 mg/Kg, oxaliplatin 3.5 mg/Kg, epothilone-B 2 or 4 mg/Kg and bortezomib 0.4 or 0.8 mg/Kg. At the end of the treatment, sensory/motor and sensory nerve conduction velocities (NCVs) were determined stimulating respectively the caudal and the digital nerves by using an electromyography apparatus. DRG and sciatic nerves were collected for the neuropathological analysis at the light and electron microscope and the morphometrical analysis of sensory neurons.

The electrophysiological study revealed that all compounds determined a statistically significant reduction in caudal NCV, while only some selected doses induced a significant impairment also of the digital NCV. These functional damages were confirmed by morphological observations describing an axonal degeneration in the sciatic nerve induced by paclitaxel, epothilone-B and bortezomib and alterations in DRG induced by platinum compounds and bortezomib. Platinum compounds determined also a somatic and nucleolar quantitative reduction-in-size of DRG sensory neurons.

These results suggest that the selected treatment schedules are able to induce both sensory/motor and pure sensory peripheral neuropathies in the mice and allow to combine the study of the antineoplastic activity and of peripheral neurotoxicity, and can be used as a reference for new anticancer drugs as well as for neuroprotection studies.

KEYWORDS: chemotherapy, peripheral neuropathy, nerve conduction velocity, sciatic nerve, dorsal root ganglia.