DIFFERENT STRAINS OF MICE ARE DIFFERENTLY SUSCEPTIBLE TO CISPLATIN-INDUCED PAINFUL PERIPHERAL NEUROPATHY (CIPN): ROLE OF PHARMACOGENOMICS?

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Even if mortality rates of genitourinary cancers patients are declining due to earlier diagnosis and increasingly aggressive antineoplastic regimens, treatment-related complications that severely compromise the patients' quality of life remain an unsolved problem. Patients treated with cisplatin often develop painful peripheral neuropathy that becomes evident after a cumulative dose of 300 mg/m^2. Cisplatin produces a symptomatic and clinically detectable sensory peripheral neuropathy characterized by distal paresthesias and numbness. In advanced stages, it may progress to severe neuropathic pain and sensory ataxia. The fact that patients receiving cisplatin differentially develop neuropathy suggests an individual variation in the drug toxicity response. Moreover, understanding the genomics of CIPN would lead to new therapeutic targets and should be useful for a molecular diagnostic screening. In this study we assessed the severity of CIPN in six mouse strains using Nerve Conduction Velocities (NCV) and Neurometer studies, morphological analysis of DRG, caudal and sciatic nerves and lumbar spinal cord and behavioral assessment of mechanical allodynia. Once the characteristics of painful peripheral neuropathy have been established in the different strains, a genome-wide association study will be performed to elucidate the genetic determinants of the variability in developing peripheral neuropathy. Cisplatin 4 mg/Kg was intraperitoneally administered twice a week for 4 weeks in CD1, Balb-c, C57BL6, FVB, DBA and AJ mice.

Cisplatin induced a significant impairment of caudal and digital NCV in AJ, Balb-c, C57BL6 and CD1 mice but not in FVB and DBA mice. Neurometer analysis, that uses neuroselective electrical stimuli to perform a quantitative assessment of the functionality of the three major subpopulations of sensory nerve fibers (A-delta, A-beta and C) revealed that large myelinated fibers (A-beta) were affected by cisplatin in Balb-c and CD1 mice starting from the 2^{nd} week of treatment, small myelinated (A-delta) only in Balb-c while small unmyelinated fibers (C) remains unaffected only in FVB and AJ mice. Moreover, cisplatin administration resulted in a significant decrease in the threshold of response to mechanical stimulation (mechanical allodynia) in Balb-c, C57BL6, CD1 and DBA starting from the first week of treatment while AJ and FVB never develop mechanical allodynia during the experimental period.

Taken together, these results demonstrate that CD1 and FVB mice were the most and least affected by cisplatin, respectively. Further genome wide association studies will allow us to investigate the differential gene expression in DRG and the spinal cord with genotyping in order to define relevant genes in CIPN.

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