CISPLATIN-INDUCED PAINFUL PERIPHERAL NEUROPATHY SEVERITY IS STRAIN-DIPENDENT IN MICE: DISSECTING THE ROLE OF PHARMACOGENOMICS

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Cisplatin is an anticancer drug employed for the treatment of several solid tumours, including testicular, ovarian, breast and lung cancers. However, treatment side effects remain an unsolved problem. Some of the patients treated with cisplatin, after a cumulative dose of 300 mg/m^2, develop a painful peripheral neuropathy (PPN) characterized by distal paresthesias, numbness, sensory ataxia and neuropathic pain. Since a different degree of the PPN severity suggests an individual variation in the drug toxicity response, the understanding of the genomics underlying PPN would lead to new therapeutic targets and to early diagnostic screening. In this study we assessed the severity of cisplatin-induced PPN in six mouse strains using Nerve Conduction Velocities (NCV), Neurometer studies, morphological analysis of DRG, caudal and sciatic nerves and lumbar spinal cord, morphometrical analysis of DRG and behavioral assessment of mechanical allodynia. 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 all except FVB and DBA mice. Moreover, cisplatin administration resulted in a significant decrease in the response to mechanical stimulation in Balb-c, C57BL6, CD1 and DBA starting from the first week of treatment while AJ and FVB never develop mechanical allodynia. Neurometer analysis, that allows a quantitative assessment of the functionality of the three major subpopulations of sensory nerve fibers (A-delta, A-beta and C), showed that large myelinated fibers (A-beta) were affected by cisplatin in Balb-c and CD1, small myelinated (A-delta) only in Balb-c while small unmyelinated fibers (C) were unaffected only in FVB and AJ mice. The morphometrical analysis revealed a nucleolar and somatic atrophy of DRG sensory neurons of CD1 but not of FVB-treated mice. 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 investigate the differential gene expression in DRG and lumbar spinal cord to define relevant genes in determining the susceptibility and severity of cisplatin-induced PPN.

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