

Evaluation of the neuro- and osteotoxicity by cisplatin in male mice

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INTRODUCTION: Cisplatin is one of the most used chemotherapeutic agents for the treatment of various types of cancer. Previous studies have reported that the use of this antineoplastic agents causes severe acute side effects in bone. This induces a state like osteoporosis. The goal of this study was to characterize the effect of the administration of cisplatin on the density and microarchitecture of trabecular bone, and the density of sensorial and sympathetic nerve fibers innervating the femur of male mice.

METHODS: All animal experiments were conducted with the approval of the committee of the Unidad Académica Multidisciplinaria Reynosa Aztlan of the Universidad Autónoma de Tamaulipas. Male ICR mice at 12 weeks old received 10 administrations of cisplatin (2.5 mg/kg, i.p.) for 2 weeks or vehicle. At 14 days post-first injection of cisplatin, animals were sacrificed by intracardiac perfusion. Then, the lower limbs were removed and processed by Micro-computed Tomography (MicroCT) and immunohistochemistry (IHC) analyses at the level of femur and tibia.

RESULTS SECTION: The analyses revealed that cisplatin-exposed mice showed a significant decrease in bone mineral density (BMD), bone volume rate (BV/TV) and trabecular number (Tb.N), and an increase in the trabecular separation in femur and tibia as compared to vehicle group. Analyses performed at the cortical in the mid-diaphyseal femur and tibia did not show significant differences between cisplatin and vehicle groups. Regarding nerve fiber profiles, there was a loss in the density of TH+ sympathetic nerve fibers, but not in CGRP+ sensory innervating the femoral periosteum.

DISCUSSION: In the present study we confirm that cisplatin resulted in a significant loss of the trabecular metaphyseal bone from the femur and tibia, which confirms what has been previously reported. We provide for the first-time evidence that cisplatin induces a denervation of sympathetic nerve fibers innervating the femoral periosteum. This model may represent a platform to understand the mechanisms behind the neuro- and osteo-toxic effects of cisplatin and thus to develop rational therapies to treat this cisplatin-induced toxicity.

SIGNIFICANCE/CLINICAL RELEVANCE:

1. Results support that cisplatin has negative effects on bone density as well as the nerve fibers innervating bone tissue
2. This model may represent an experimental platform to evaluate new therapies to treat the neuro- and osteo-toxicity induced by cisplatin.