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Mitoxantrone-induced neurotoxicity in CD-1 mice

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Resumo

Introduction: Mitoxantrone (MTX) is a topoisomerase II inhibitor used to treat a wide range of tumors and multiple sclerosis [1]. Nevertheless, its brain toxicity is poorly understood. **Objectives:** Evaluation of the underlying neurotoxic mechanisms of a clinically relevant cumulative dose of MTX in the brain of adult male CD-1 mice. **Materials and Methods:** Three-month-old male CD-1 mice received bi-weekly intraperitoneal administrations of MTX for 3 weeks, to mimic human cycles of chemotherapy, until they reached a total cumulative dose of 6 mg/kg of MTX. They were sacrificed one week later. In the whole brain, biomarkers of oxidative stress, neuronal damage, apoptosis, and autophagy were evaluated. Coronal sections of fixed brains were used for immunofluorescent detection of proteins of neuronal damage in the prefrontal cortex (PFC) and hippocampal formation (HF). In the latter area, volume, and the total number of glial fibrillary acid protein (GFAP)-immunoreactive (ir) astrocytes were determined. Statistical analyses was performed by t-test with Welch's correction. **Results:** In the whole brain, our results demonstrated that MTX induced redox imbalance, namely: a tendency to decrease the glutathione levels, increase in endothelial nitric oxide synthase and reduced manganese superoxide dismutase expression. Brain metabolism was also altered as seen by diminished adenosine triphosphate synthase subunit β expression. MTX administration also caused increased autophagic protein microtubule-associated protein light chain 3 II and a tendency to decrease p62 expression. Postsynaptic density protein 95 expression decreased. Regarding the regional analysis, a reduction in volume was observed in the dentate gyrus (DG) and CA1 region of the HF. GFAP-ir astrocytes increased in all regions of the HF except in the DG, suggesting extensive astrogliosis. Apoptotic marker Bax increased in the PFC and CA3 regions, whereas p53 decreased in all brain areas evaluated. In the PFC, MTX caused hyperphosphorylation of Tau. **Conclusions:** MTX causes damage in the brain of adult CD-1 mice in a clinically relevant cumulative dose. There is a need for further studies, as its use is increasing specially among multiple sclerosis patients besides cancer patients.

Keywords: mitoxantrone; neurotoxicity; chemotherapy; chemobrain; brain.

References:

[1] Dias-Carvalho A, Ferreira M, Reis-Mendes A, Ferreira R, Bastos ML, Fernandes E, Sá SI, Capela JP, Carvalho F, Costa VM. Chemobrain: Mitoxantrone-induced oxidative stress, apoptotic and autophagic neuronal death in adult CD-1 mice. Arch Toxicol. Accepted (2022).

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