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Long-Term Neurotoxic Effects of Mitoxantrone in Aged Mice: Modulation of Neuroinflammatory and Apoptotic Pathways

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Abstract

Background: Chemotherapy-induced cognitive dysfunction ("chemobrain") is an increasingly relevant clinical issue among cancer survivors. The neurotoxic effects of mitoxantrone (MTX), particularly in the elderly, remain poorly understood. **Objective:** This study aimed to evaluate the long-term neurotoxic effects of a clinically relevant cumulative dose of MTX in aged mice. **Methods:** Male CD-1 mice (18–20 months) received MTX (4.5 mg/kg, cumulative dose) administered biweekly via intraperitoneal injection over three weeks. Two months after the final administration, brains were collected. Immunofluorescence was used to assess proteins associated with apoptosis, inflammation, and neuronal damage in the prefrontal cortex (PFC) and the hippocampal formation (HF). Glutathione-related compounds were analysed, and whole-brain metabolomics is ongoing. Statistical comparisons were performed using an unpaired t-test with Welch's correction. **Results:** MTX induced region-specific alterations in neurotoxic pathways. In the HF, p53 levels decreased in the hilus and increased in CA3, while Bax and Bcl-2 showed a decreasing trend. In the PFC, apoptosis-inducing factor (AIF) increased significantly. TNF-α levels were elevated in the PFC, with increasing trends in hippocampal regions. Hyperphosphorylated tau levels were significantly increased in both PFC and HF. Glutathiolomic analysis revealed a tendency toward decreased cysteinylglycine levels. **Conclusions:** A clinically relevant cumulative dose of MTX induces persistent and region-specific modulation of neuroinflammatory and apoptotic pathways in the aged brain, highlighting increased susceptibility to MTX-induced neurotoxicity.

Keywords: mitoxantrone; neurotoxicity; ageing

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