NTOX-04. INVESTIGATION OF N-ACETYLCYSTEINE FOR THE PREVENTION OF CISPLATIN CHEMOTHERAPY-RELATED COGNITIVE IMPAIRMENTS

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OBJECTIVES: Chemotherapy-related cognitive impairment (CRCI) is a major clinical problem, which diminishes the quality of life of cancer sur-

vivors. We focus on the neurocognitive impairments provoked by cisplatin, a chemotherapy agent widely used as treatment for various malignancies including ovarian, testicular, head and neck cancers, and pediatric brain tumors. More than 30% of advanced ovarian cancer patients develop CRCI during and after cisplatin-based chemotherapy. We examined mitochondrial dysfunction as a mechanism underlying cisplatin CRCI, and the ability of the antioxidant N-acetylcysteine to mitigate these toxicities in a rat model, and *in-vitro* in cultured rat hippocampal neurons and neural stem/progenitor cells (NSC). **METHODS:** We examined the effects of cisplatin on neuronal morphology, apoptosis, and cognition in rats. We assessed the effects of cisplatin on mitochondrial respiratory function, reactive-oxygen species (ROS) production, caspase-9 activation, and glutathione levels *in-vitro*. **RESULTS:** Cisplatin reduced neuronal dendritic branching and spine density and induced apoptotic cell death in the rat hippocampus. Chronic cisplatin treatment impaired cognitive function; this impairment was mitigated by N-acetylcysteine administration. *In-vitro,* cisplatin damaged mitochondrial DNA, impaired respiratory activity, elevated ROS levels, and depleted glutathione. N-acetylcysteine mitigated cisplatin-induced neural ROS levels and glutathione depletion, apoptotic cell death, and neuronal post-synaptic density-95 puncta loss, while not interfering with cisplatin's anti-cancer effect in two ovarian cancer cell lines when administered 10 h following cisplatin. **DISCUSSION:** The cognitive deficits caused by cisplatin in rats result from the loss of excitatory synapses and dendritic spines that anchor them, as well as from injury to mature and developing neurons. This neuronal toxicity derives from mitochondrial damage. Importantly, treatment with N-acetylcysteine mitigates cisplatin-induced neurotoxicity and cognitive deficits. We are planning a Phase I study to examine if NAC administration to ovarian cancer patients receiving cisplatin is safe, and if it ameliorates the cognitive deficits previously described in this patient population.