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Anticancer drugs and their impact on chemobrain development: an *in vitro* investigation

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Abstract

Background: Cancer incidence has been increasing worldwide, over the past few years. “Chemobrain” refers to alterations in cognitive function after cancer treatment, including memory deficits and reduced attention capacity [1]. The blood-brain barrier restricts the entry of certain anticancer drugs into the brain. However, "chemobrain" can also arise from factors extending far beyond direct drug exposure to the brain [1]. **Objective:** This work aims to access how neurons are affected by different anticancer drugs, such as doxorubicin (DOX), methotrexate (MTX) and sunitinib (SUN), all known to cause clinical cognitive deficits. **Methods:** Differentiated human neuroblastoma cells (SH-SY5Y) were exposed for 24h or 48h to clinically relevant concentrations of DOX (0.1-10 µM), SUN (1-10 µM) and MTX (5 and 10 µM). Two classical cytotoxicity assays (neutral red uptake and MTT reduction) were performed at the end of the exposure times. In a different paradigm, autophagy inhibitors [3-methyladenine (3-MA) or chloroquine (CLQ)] were used to determine their effects on SUN cytotoxicity. **Results:** DOX led to concentration-dependent cytotoxicity, which was amplified in the longest exposure time in both assays. On the other hand, MTX caused significant toxicity at 5 µM and 10 µM, which was time-dependent but not concentration-dependent in the MTT reduction assay. In the NR uptake assay, toxicity was seen only on the longest incubation time. Regarding SUN, both assays revealed a time- and concentration-dependent cytotoxicity. For SUN, cells appeared with yellow inclusions and autophagy modulators were used. As for autophagy inhibitors, results were dissimilar, since for SUN 10 µM, 3-MA was partially protective, whereas CLQ significantly increased SUN’s cytotoxicity in both assays at 24h. **Conclusions:** These findings highlight DOX’s, MTX’s and SUN’s cytotoxicity in neurons, with DOX and SUN being equally potent. Additionally, autophagy inhibitors suggest dysregulation of autophagy as a possible mechanism underlying SUN´s neurotoxicity. Nonetheless, further research is needed.

Keywords: chemobrain; chemotherapy, neurotoxicity; neurons; cancer

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