ARSENIC TRIOXIDE ENHANCES THE ANTITUMOR ACTIVITY OF CISPLATIN IN BLADDER TUMOR CELL LINE MODELS, VIA INHIBITION OF FA/BRCA REPAIR PATHWAY.

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Arsenic trioxide (ATO) is an inorganic arsenic derivative administered to treat certain types of cancers, although its adverse side-effects and unknown mechanism(s) of action may confine its therapeutic effect in clinical practice.

This work aims to determine whether ATO is able to potentiate the antitumor effects of the ICL-inducer cisplatin (CDDP) in bladder cancer cells via FA/BRCA disruption. Thus, SW800, 5637 and T24 cell lines were co-treated with different doses of ATO and CDDP, alone or in combination. The integrity of the FA/BRCA repair pathway was analyzed after the treatments, together with cell viability and several characteristic bladder cancer features.

Our results show that ATO co-treatments reduce the cellular capacity to trigger the CDDP-dependent FA/BRCA function in all cases, as indicated by a significant decrease in the FANCD2 ubiquitination and foci formation. Consequently, combinations of ATO and CDDP synergistically induce toxicity in bladder cancer cells, along with a significant decrease in SW800, 5637 and T24 anchorage-independent cell growth, migration capacity, and secretion of matrix metalloproteinases.

This is the first study demonstrating the potential beneficial effects of ATO and CDDP combined therapy via FA/BRCA disruption.