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Sensitizing Hypoxic Small Cell Lung Cancer Cells to Radiation and Hydrogen Peroxide-Producing Agents Using CuATSM

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BACKGROUND: Cancer cells have increased steady state levels of reactive oxygen species (ROS; O₂^{•-} and H₂O₂) compared to normal cells. It has been proposed that using redox active agents that further increase ROS levels will result in selective cancer cell death. This metabolic frailty can be targeted using drugs deemed safe for human use, ascorbate (ASC) and disulfiram (DSF), via a mechanism of H₂O₂ production. CuATSM is a drug being used in clinical trials to treat ALS disease. Imaging studies have shown that CuATSM preferentially concentrates in hypoxic tissues, releasing its Cu after entering cells. Copper (Cu) can participate in oxidation reactions that result in highly toxic hydroxyl radicals. Tumors often have areas of hypoxic tissue that exhibit resistance to ionizing radiation (IR). Our hypothesis is that CuATSM can be used to sensitize hypoxic regions of tumors to IR, ASC and/or DSF.

METHODS: H₂O₂ flux after addition of ASC or DSF was measured in small cell lung cancer (SCLC) cells DMS53 using the 3-aminotriazole method. The Cu uptake of these cells was measured in normoxia and hypoxia after treatment with CuATSM. DMS53 and DMS273 (SCLC lines) were treated with ASC, CuATSM, and/or DSF+CuSO₄ at varying oxygen tensions with and without IR and clonogenic assays were performed.

RESULTS: Pharmacologically relevant dosing of DSF and ASC resulted in significantly higher fluxes of H₂O₂ compared to control. Both DSF and ASC enhanced IR clonogenic cell death in SCLC lines. Treatment with CuATSM resulted in increased intracellular Cu and enhanced cell death from ASC and IR in hypoxic conditions.

CONCLUSION: These observations support the hypothesis that the differences in steady-state level of ROS in small cell lung cancer cells can be exploited to develop effective therapies using ASC and DSF. Furthermore CuATSM can enhance responses in hypoxic tumor tissues to both IR and ASC.