Disulfiram

Disulfiram has shown promising activity including proteasome inhibitory properties and synergy with temozolomide in preclinical glioblastoma (GBM) models.

DSF is a relatively nontoxic drug used for more than sixty years in the treatment of chronic alcoholism with the ability to readily cross the blood-brain barrier. Repurposing DSF for use as an anticancer drug in general has recently become of interest because of its preclinically described anticancer effects against various human cancers. Interestingly, a number of these effects were shown to be copper (Cu)-dependent.

The purpose of a study of Koh from the Seoul National University Children's Hospital, Korea, was to determine the effect of disulfiram (DSF), an aldehyde dehydrogenase inhibitor, on in vitro radiosensitivity of glioblastoma cells with different methylation status of O6-methylguanine-DNA methyltransferase (MGMT) promoter and the underlying mechanism of such effect.

Five human glioblastoma cells (U138MG, T98G, U251MG, U87MG, and U373MG) and one normal human astrocyte (NHA) cell were cultured and treated with DSF or 6MV x-rays (0, 2, 4, 6, 8 Gy). For combined treatment, cells were treated with DSF before irradiation. Surviving fractions fit from cell survival based on colony forming ability. Apoptosis, DNA damage repair, and cell cycle distribution were assayed by Western blot for cleaved caspase-3, γH2AX staining, and flow cytometry, respectively.

DSF induced radiosensitization in most of the glioblastoma cells, especially, in the cells with radioresistance as wildtype unmethylated promoter (MGMT-wt), but did not in normal NHA cell. DSF augmented or induced cleavage of caspase-3 in all cells after irradiation. DSF inhibited repair of radiation-induced DNA damage in MGMT-wt cells, but not in cells with methylated MGMT promoter (MGMT-meth). DSF abrogated radiation-induced G2/M arrest in T98G and U251MG cells.

Radiosensitivity of glioblastoma cells were preferentially enhanced by pre-irradiation DSF treatment compared to normal cell, especially radioresistant cells such as MGMT-wt cells. Induction of apoptosis or inhibition of DNA damage repair may underlie DSF-induced radiosensitization. Clinical benefit of combining DSF with radiotherapy should be investigated in the future [1)].

Huang et al., report the final results of a phase I study including an additional dose-expansion cohort of disulfiram with concurrent copper. The phase I study consisted of an initial dose-escalation phase of disulfiram 500-1000 mg daily during adjuvant temozolomide, followed by a dose-expansion phase of disulfiram 500 mg daily with copper 2 mg three times daily. Proteasome inhibition was assessed using fluorometric 20S proteasome assay on peripheral blood cell. A total of 18 patients were enrolled: 7 patients received 500 mg disulfiram, 5 patients received 1000 mg disulfiram, and 6 patients received 500 mg disulfiram with copper. Two dose-limiting toxicities occurred with 1000 mg disulfiram. At disulfiram 500 mg with or without copper, only 1 patient (7%) required dose-reduction during the first month of therapy. Addition of copper to disulfiram did not increase toxicity nor proteasome inhibition. The median progression-free survival was 4.5 months (95% CI 0.8-8.2). The median overall survival (OS) was 14.0 months (95% CI 8.3-19.6), and the 2-year OS was 24%. The MTD of disulfiram at 500 mg daily in combination with adjuvant temozolomide was well tolerated by GBM patients, but 1000

mg daily was not. Toxicity and pharmacodynamic effect of disulfiram were similar with or without concurrent copper. The clinical efficacy appeared to be comparable to historical data. Additional clinical trials to combine disulfiram and copper with chemoradiotherapy or to resensitize recurrent GBM to temozolomide are ongoing [2].

The purpose of a paper was to review the existing literature surrounding preclinical and clinical data on the effects of DSF -alone or in combination with Cu- in GBM. In addition, Karamanakos et al. present the first case of a GBM patient safely treated with DSF/Cu combination along with standard therapy exhibiting remarkably increased progression-free (PFS) and overall survival (OS) [3].

1)
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2)
Huang J, Campian JL, Gujar AD, Tsien C, Ansstas G, Tran DD, DeWees TA, Lockhart AC, Kim AH. Final results of a phase I dose-escalation, dose-expansion study of adding disulfiram with or without copper to adjuvant temozolomide for newly diagnosed glioblastoma. J Neurooncol. 2018 Jan 27. doi: 10.1007/s11060-018-2775-y. [Epub ahead of print] PubMed PMID: 29374809.
3)
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