Etomoxir for glioblastoma

The importance of fatty acid oxidation (FAO) in the bioenergetics of glioblastoma (GBM) is being realized. Etomoxir (ETO), a carnitine palmitoyltransferase 1 (CPT1) inhibitor exerts cytotoxic effects in GBM, which involve interrupting the FAO pathway.

Shim et al. from Seoul hypothesized that FAO inhibition could affect the outcomes of current standard temozolomide (TMZ) chemotherapy against GBM.

The FAO-related gene expression was compared between GBM and the tumor-free cortex. Using four different GBM tumorspheres (TSs), the effects of ETO and/or TMZ were analyzed on cell viability, Citric acid cycle intermediates, and adenosine triphosphate (ATP) production to assess metabolic changes. Alterations in tumor stemness, invasiveness, and associated transcriptional changes were also measured. A mouse orthotopic xenograft model was used to elucidate the combinatory effect of TMZ and ETO.

GBM tissues exhibited overexpression of FAO-related genes, especially CPT1A, compared to the tumor-free cortex. The combined use of ETO and TMZ further inhibited the Citric acid cycle and ATP production more than single uses. This combination treatment showed superior suppression effects compared to treatment with individual agents on the viability, stemness, and invasiveness of GBM TSs, as well as better downregulation of FAO-related gene expression. The results of the in vivo study showed prolonged survival outcomes in the combination treatment group.

ETO, an FAO inhibitor, causes a lethal energy reduction in the GBM TSs. When used in combination with TMZ, ETO effectively reduces GBM cell stemness and invasiveness and further improves survival. These results suggest a potential novel treatment option for GBM [1)].

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[1)]

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