Aldehyde dehydrogenase 1A1--a new mediator of resistance to temozolomide in glioblastoma.

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Abstract

Implementation of chemotherapy with the drug temozolomide increased the overall survival of patients with glioblastoma multiforme (GBM; WHO grade IV), in particular when the O(6)-methylguanine DNA methyltransferase (MGMT) promoter is epigenetically silenced. Nevertheless, the prognosis remains poor, and relapse in GBM occurs regularly. This clinical behavior seems to be due to the existence of a therapy-resistant subpopulation of cells that induce tumor regrowth. The objective of this work was to analyze the role of aldehyde dehydrogenase (ALDH) 1A1 in mediating temozolomide resistance and its value as a predictor of clinical outcome in GBM patients. Nine GBM cell lines were treated with temozolomide alone or in combination with 4-diethylaminobenzaldehyde (DEAB), an inhibitor of ALDH1A1, or with ALDH1A1 short hairpin (sh)RNA. ALDH1A1 expression and MGMT status of 70 primary GBM patients were correlated with median survival. ALDH1A1 overexpression predicted temozolomide resistance in vitro. Sensitivity of ALDH1A1 positive/MGMT-positive cells to temozolomide could be restored by inhibition of ALDH1A1 by DEAB or by knockdown with shRNA, as indicated by increased cytotoxicity, reduced clonogenicity, and accumulation in the G2/M cell-cycle phase. The prognosis of patients with a high level of ALDH1A1 expression was poor compared with that of patients with low levels (P < .0001). ALDH1A1 is a new mediator for resistance of GBM to temozolomide and a reliable predictor of clinical outcome and may serve as a potential target to improve treatment of human GBM.