

Answer 1:

Bibliographic Information

Potentiation of lonidamine and diazepam, two agents acting on mitochondria, in human glioblastoma treatment. Miccoli, Laurent; Poirson-Bichat, Florence; Sureau, Franck; Goncalves, Rui Bras; Bourgeois, Yveline; Dutrillaux, Bernard; Poupon, Marie-France; Oudard, Stephane. Laboratoire de Cytogenetique Moleculaire et Oncologie, Institut Curie, Section de Recherche, Paris, Fr. Journal of the National Cancer Institute (1998), 90(18), 1400-1406. Publisher: Oxford University Press, CODEN: JNCIEQ ISSN: 0027-8874. Journal written in English. CAN 130:47125 AN 1998:633690 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Cellular metab. in glioblastoma multiform, the most common primary brain tumor in humans, is characterized by a high rate of aerobic glycolysis that is dependent on mitochondria-bound hexokinase. Moreover, high levels of glucose utilization and tumor aggressiveness in glioblastoma are assocd. with a high d. of mitochondrial benzodiazepine receptors. The authors sought to inhibit glioblastoma metab. by simultaneously inhibiting hexokinase with lonidamine and binding benzodiazepine receptors with diazepam. Cellular glioblastoma metab. in five glioblastoma cell lines was assessed in vitro by measuring cell proliferation (by use of a tetrazolium-based colorimetric assay, measurement of DNA synthesis, and assessment of cell cycle distribution), by measuring membrane fluidity (by fluorescence polarization measurement of cells stained with a fluorescent probe), and by measuring changes in intracellular pH. Immunodeficient nude mice bearing s.c. xenografts of human glioblastoma cells were used to assess the antitumor activities of lonidamine and diazepam; the mice were treated twice daily with lonidamine (total daily dose of 160 mg/kg body wt.) and/or diazepam (total daily dose of 1 mg/kg body wt.) for 10 consecutive days. When used in combination, the two drugs had a stronger effect on glioblastoma cell proliferation and metab. in vitro than did either agent used alone. In vivo, the combination of lonidamine and diazepam was significantly more effective in reducing glioblastoma tumor growth than either drug alone (two-sided $P < .01$, Mann-Whitney U test, comparing growth of treated tumors with that of untreated tumors); this tumor growth retardation was maintained as long as treatment was given. The combination of lonidamine and diazepam-drugs that target two distinct mitochondrial sites involved in cellular energy metab.-potentiates the effects of the individual drugs and may prove useful in the treatment of human glioblastomas.