Noninvasive detection of temozolomide in brain tumor xenografts by magnetic resonance spectroscopy - DTU Orbit (02/12/2018)

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Poor drug delivery to brain tumors caused by aberrant tumor vasculature and a partly intact blood-brain barrier (BBB) and blood-brain tumor barrier (BTB) can significantly impair the efficacy of chemotherapy. Determining drug delivery to brain tumors is a challenging problem, and the noninvasive detection of drug directly in the tumor can be critically important for accessing, predicting, and eventually improving effectiveness of therapy. In this study, in vivo magnetic resonance spectroscopy (MRS) was used to detect an anticancer agent, temozolomide (TMZ), in vivo in murine xenotransplants of U87MG human brain cancer. Dynamic magnetic resonance imaging (MRI) with the low-molecular-weight contrast agent, gadolinium diethylenetriaminepentaacetic acid (GdDTPA), was used to evaluate tumor vascular parameters. Carbon-13-labeled TMZ ([C-13]TMZ, 99%) was intraperitoneally administered at a dose of similar to 140 mg/kg (450 mg/m(2), well within the maximal clinical dose of 1000 mg/m(2) used in humans) during the course of in vivo MRS experiments. Heteronuclear multiple-quantum coherence (HMQC) MRS of brain tumors was performed before and after i.p. administration of [C-13]TMZ. Dynamic MRI experiments demonstrated slower recovery of MRI signal following an intravenous bolus injection of GdDTPA, higher vascular flow and volume obtained by T-2*-weighted MRI, as well as enhanced uptake of the contrast agent in the brain tumor compared with normal brain detected by T-1-weighted MRI. These data demonstrate partial breakdown of the BBB/BTB and good vascularization in U87MG xenografts. A [C-13] TMZ peak was detected at 3.9 ppm by HMOC from a selected volume of about 0.15 cm(3) within the brain tumor with HMOC pulse sequences. This study clearly demonstrates the noninvasive detection of [C-13]TMZ in xenografted U87MG brain tumors with MRS. Noninvasive tracking of antineoplastic agents using MRS can have a significant impact on brain tumor chemotherapy.

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