

Magnetic Resonance Imaging Study of Carmustin and Sorafenib antitumor efficacy evaluation in Orthotopic Human Glioblastoma Models Xenografted in Nude Rats.

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Glioblastoma is the most aggressive subtype of brain tumors. Monitoring changes in glioma microvasculature should help to evaluate the efficacy of new antitumor therapy. The aim of this study was to assess the sensitivity of magnetic resonance imaging (MRI) biomarkers to the antitumor activity of Carmustin and Sorafenib in human glioblastoma model.

Nude rats were orthotopically injected at D0 with U87-MG glioma cells. Rats were randomized at D14 to receive either one injection of 10 mg/kg Carmustin (BCNU) i.v. or 14 daily administrations of 100 mg/kg Sorafenib (SORA) p.o. or no treatment (CTL). Rat survival was monitored daily. Blood volume (BV), vessel size index (VSI), apparent diffusion coefficient (ADC) and blood brain barrier permeability to a contrast agent (BBB perm.) were mapped, in tumor, at 2.35T one day before treatment and 1, 4 and 14 days after treatment onset (respectively D13, D15, D18 and D28). Tumor volumes were measured on T₂-weighted images. VSI/BV and BBB perm. parameters were computed from T₂, T₂* and T₁-weighted images using an intravascular contrast agent (ferumoxtran-10) and P846, a Gd-based contrast agent, both provided by Dr P. Robert, (Guerbet/AMAG Pharmaceuticals). In each group, the same four rats were imaged at each time point. Four additional rats were also imaged per time point and euthanized at the end of the imaging session for Collagen IV immunohistochemistry studies.

SORA and BCNU treatments strongly inhibited the tumor growth of both models (T/C=25% and 6% at D28 respectively). At D28, ADC in SORA and BCNU groups were 21 and 23% higher than in the CTL group, respectively. At any time, VSI did not differ between BCNU and CTL groups. VSI in SORA group was significantly increased by 24 to 42% when compared to CTL group at D15 and D28, respectively. BV was not modified by BCNU treatment but was strongly decreased by SORA treatment (4.6±0.5 at D13 to 1.86±0.2% at D28). While BBB remained permeable in BCNU and CTL groups, SORA-treated tumor became impermeable to P846 as early as 4 days after treatment onset. Despite tumor growth inhibition and vasculature modification, BCNU and SORA displayed a moderate increase of U87-MG tumor-bearing rats survival (ILS=18% and 23%, respectively). Collagen IV staining demonstrate a strong decrease of vessel number in the SORA-treated tumors.

MRI demonstrated a tumor growth inhibition induced by SORA and BCNU treatments despite the poor effect of these 2 treatments on the survival of U87-MG-bearing rats. ADC appeared sensitive to both treatment but VSI and BV were sensitive to the effect of SORA treatment only. These results are consistent with the anti-angiogenic activity of SORA (confirmed by Collagen IV staining). Together, these results indicate that VSI, BV and ADC markers measured by MRI would be of value to combine anti-angiogenic with cytotoxic therapies in glioblastomas.