

DCE-MRI in rat gliomas under therapy with temozolomide and a nitric oxide donor

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Introduction

The response of gliomas to systemic chemotherapy is limited by the blood-tumor barrier which impairs the drug delivery to brain tumors. Nitric oxide (NO) is involved in the regulation of vasodilation, cerebral blood flow, and vascular permeability. Exogenous NO delivered by an NO donor compound increases the vascular permeability of the blood-tumor barrier and can enhance the efficacy of chemotherapy (1). In this DCE-MRI study we investigated the effect of a concomitant therapy with temozolomide (standard chemotherapy drug for gliomas) and the NO donor JS-K on perfusion and vascular permeability of rat gliomas *in vivo*.

Methods

Nude rats (n=10/group) were inoculated with 5×10^5 U87 cells into the right striatum. Treatment with JS-K (3.5 $\mu\text{mol/kg}$ i.v.), temozolomide (TMZ, Temodal, 3.9 mg/rat i.p.), or with a combination was performed 3x/week starting on day 5. JS-K is a diazeniumdiolate activated to release high levels of NO by glutathione-S-transferase enzymes that are overexpressed in gliomas (2). MRI scans were performed on 5 rats per group (3 treatment groups + control group) on day 12, 1 week after initiation of treatment. T₂-weighted multislice RARE scans were used to localize the tumors and to assess tumor volume (20 slices of 1 mm thickness, in-plane resolution 0.12x0.12 mm, TE/TR 20/4200 ms). Series of DCE-MR images were acquired pre- and post-injection (i.v.) of the contrast agent (CA) Gd-DTPA (Magnevist, Bayer-Schering; 0.1 mmol Gd/kg) with an inversion recovery (IR) TrueFISP sequence (3) (1 slice of 2 mm thickness, in-plane resolution 0.20x0.26 mm, TE/TR 1.45/2.91 ms, 10 TIs: 1101...1918 ms, temporal resolution 6 s, 120 scans). Quantitative T₁ values and CA concentrations were calculated from the DCE-MRI data. The initial area under the CA

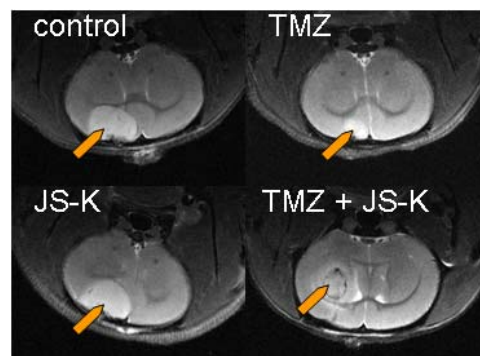


Fig. 1: RARE images of gliomas (arrows), one from each treatment group

concentration curve iAUC in the central slice of the glioma was calculated (0-60 s after CA injection) and normalized to iAUC in the contralateral brain (reference region). To assess the acute effect of JS-K on the blood-tumor barrier DCE-MRI was repeated in n=7 rats (4 rats of the JS-K group) or saline (3 control rats).

Results

Injection of JS-K between two DCE-MRI experiments led to a significant increase in norm. iAUC (see Fig. 2). The drop in T₁ (before first vs. before second CA injection) was significantly larger after JS-K than after saline injection.

After 1 week of treatment there was no difference in tumor volume between control and JS-K rats whereas it was significantly smaller for TMZ and TMZ+JS-K rats. Tumors treated with TMZ+JS-K were surrounded by hyperintense areas on T₂ scans, most likely due to a more prominent edema formation (see Fig. 1). Norm. iAUC was significantly lower in the TMZ and TMZ+JS-K groups as in controls (see Fig. 3). There was no difference in T₁ (before CA injection) between the groups.

Discussion

The acute effect of JS-K led to an increased CA content in tumors due to increased blood-tumor barrier permeability and/or blood flow as demonstrated by DCE-MRI pre and post JS-K injection. JS-K alone showed no therapeutic effect *in vivo*, unlike in previous studies *in vitro* (2). We found a significant effect of TMZ and TMZ+JS-K treatment versus the control animals, however there was no benefit after 1 week of the concomitant therapy TMZ+JS-K compared to TMZ alone. Tumor size and tumor perfusion and/or permeability assessed with DCE-MRI were similar in these two groups. Whether this is due to a maximized effect of TMZ alone, or due to secondary effects of JS-K in the *in vivo* setting remains to be clarified by histology.

References

1. Weyerbrock A et al., J Neurosurg 99:728, 2003. 2. Shami PJ et al., Mol Cancer Ther 2:409, 2003. 3. Weidensteiner C et al., JMRI 24:646, 2006.

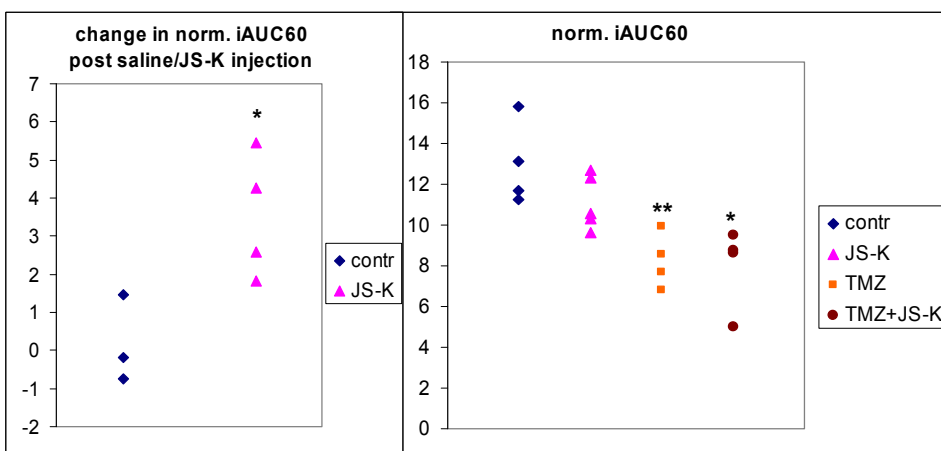


Fig. 2: Acute effect of JS-K: Change in normalized iAUC post vs. pre injection of JS-K or saline. * p<0.05 t-test compared to control

Fig. 3: Effect after 1 week of treatment: Normalized iAUC of all rats. * p<0.05, **p<0.01 t-test compared to control