

Longitudinal evaluation of HSV brain tumor therapy using diffusion tensor MR imaging

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BACKGROUND

G207 is a modified type-1 herpes simplex virus (HSV) that has been genetically engineered to replicate in and kill cancer cells while sparing normal cells. Its unique properties allow it to be delivered directly into brain tumors without harm to surrounding healthy tissue¹. Assessment of G207 treatment response currently relies on evaluating changes in tumor morphology provided by conventional anatomic magnetic resonance imaging (MRI). However, it is believed that changes in the microscopic cellular environment in malignant brain tumors following the initiation of treatment occur before tumor volume regression. Therapeutic assessment would benefit from an imaging modality that could measure pathological changes at the cellular level. Magnetic resonance diffusion tensor imaging (DTI) is a non-invasive imaging modality used to study water diffusion *in vivo*². The magnitude and the direction of water diffusion can be measured by DTI via parameters such as mean diffusivity (MD) and fractional anisotropy (FA). Given the inherent dependence on water molecules, DTI could provide microscopic tissue information such as cell density. Earlier reports^{3,4} have suggested that MD and FA in malignant brain tumors are inversely and positively correlated to cellularity respectively. The purpose of the present study was to investigate MD and FA values as surrogate markers for quantitative efficacy evaluation in a clinical trial undertaken by the UAB Brain Tumor SPORE and Medigene AG to evaluate the effects of G207 given in conjunction with radiation.

MATERIALS AND METHODS

Diffusion tensor images of brain tumor patients were acquired on a 3T MRI scanner (Intera, Philips Medical Systems, Cleveland OH) with a SENSE head coil. The diffusion single-shot EPI sequence with diffusion gradients applied in 15 directions was used. The other imaging parameters were as follows: TR/TE=3250 ms/88 ms, FOV 230mm, slice thickness/gap=4mm/1mm, 24 Slices, b value=1000 s/mm², matrix 256x256. Three patients with malignant brain tumors were imaged using conventional anatomic and DT MRI before initiation of treatment. Additional images were acquired longitudinally at 1 day, 4 days, and 28 days after treatment. Changes of mean diffusivity (MD) and fractional anisotropy (FA) in the tumor margins were calculated using a concentric annular model⁵. Post processing was performed using custom-written MATLAB (The MathWorks Inc., Natick, MA) programs. T1 weighted post-contrast images were used to compute tumor volumes. All imaging studies were approved by the University of Alabama at Birmingham Institutional review board.

RESULTS

The tumor volumes, mean MD, and FA are presented in Table 1. All patients show a decrease in mean FA and two of the three patients showed an increase in MD. These results are consistent with oncolytic activity suggesting an anti-tumor effect of the injected virus. Patient 3 responded to therapy demonstrating a decrease in tumor volume and an increase in MD.

Table 1: Tumor Volumetrics and DTI indices

Patient	Study	Tumor Volume (cc)*	Mean MD (mm ² /s)	Mean FA
1	Baseline	100.99	1.10×10 ⁻³	0.24
	Follow up	135.62	1.17×10 ⁻³	0.20
2	Baseline	72.36	1.53×10 ⁻³	0.30
	Follow up	71.96	1.30×10 ⁻³	0.26
3	Baseline	12.88	1.10×10 ⁻³	0.35
	Follow-up	8.17	1.15×10 ⁻³	0.30

CONCLUSION

Tumor volume alone is not sufficient in assessing therapy response, as evidenced by patient 2. Mean diffusivity complements tumor volume in evaluating response to G207-therapy, while our preliminary results indicate that FA does not correlate with clinical response. Diffusion tensor imaging is a valuable research tool in tracking physiological parameters which may reflect tumor cellularity. Indices such as mean diffusivity may serve as early surrogates of anti-tumor response.

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