An MRI Determination of Vascular Transfer Constant Predicts Response to Therapy in a Cerebral Glioma Model

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Introduction: A technique for measuring vascular permeability using MRI detection of contrast agent concentration has been developed, validated, and identified as to operating characteristics (1,2). The technique's demonstrated ability to measure changes in vascular permeability in response to dexamethasone (3) suggested that other clinically significant treatments might produce changes in vascular parameters. This hypothesis was tested in a treatment model in experimental cerebral glioma (U251n, a primary human glioma cell line) in nude rats. This model is unique in that two very closely related treatment paradigms produce, in the first case, complete remission (8 hrs between drug and radiotherapy - RT), and in the second case, only a moderately extended survival time (1 hr between Cilengitide and RT).

Methods: MRI imaging utilized a 7 Tesla, 12 cm (clear bore) Magnex magnet with actively shielded gradients of 250 mT/m, 100 µs risetimes, interfaced with a Bruker Avance console running Paravision V2.1.1. RF coils were volume resonator for transmission, and a 2 cm surface coil for reception. All MR sequences used a 32 mm FOV. Contrast agent (CA) concentration was followed via a T-One by Multiple Read Out Pulses (TOMROP) (4) sequence. Following each inversion of the longitudinal magnetization by a non-selective adiabatic pulse, one phase-encode line of 24 small-tip-angle (~18° shaped pulses) gradient-echo images (TE 4 ms) was acquired at 50 ms intervals, for a total recovery time of 1200 ms with a 2.2 sec interval between each inversion. Matrix size was 128X64, three 2 mm slices. After two initial baseline TOMROP studies, Gadomer (Schering AG) was administered 250 µmol/kg in a 0.6 ml dose over the first minute of the third TOMROP study, and then followed by 9 subsequent studies over a total of 25 minutes. Pre-contrast studies included single-slice ASL blood flow (matrix 64x64), high-resolution T1-weighted (TR/TE = 1000/7.5, matrix 256/192, 27 0.5 mm slices, 4 accumulations), T2-weighted imaging (TR/TE = 2000/10 ms, 3 CPMG echoes, matrix 256X192 seventeen 0.5 mm slices, 4 accumulations), and trace diffusion-weighted imaging and an apparent diffusion coefficient (ADC) measurement: PGSE (TR/TE=1500ms/ 40ms, b-values=10, 400 and 800 s/mm^2, thirteen 1 mm slices,128X128 matrix). One high-resolution T1 study was performed after the last of the TOMROP studies, about 25 minutes post-injection of CA.

Thirteen nude rats implanted with an intracerebral U251n cerebral glioma were studied in the MRI protocol described above. The animal was then removed from the magnet and administered Cilengitide (4 mg/kg I.P.). After an interval of either 1 hr (partial response group) or 8 hr (complete response), the animals were stereotactically irradiated using a 6 MV Varian Clinac in a single dose of about 20 Gy to the tumor. After irradiation, the animal was returned to its cage and the MRI imaging protocol was repeated at times of 12 (n=13), 36 (n= 8), and 84 (n= 8) hrs after RT.

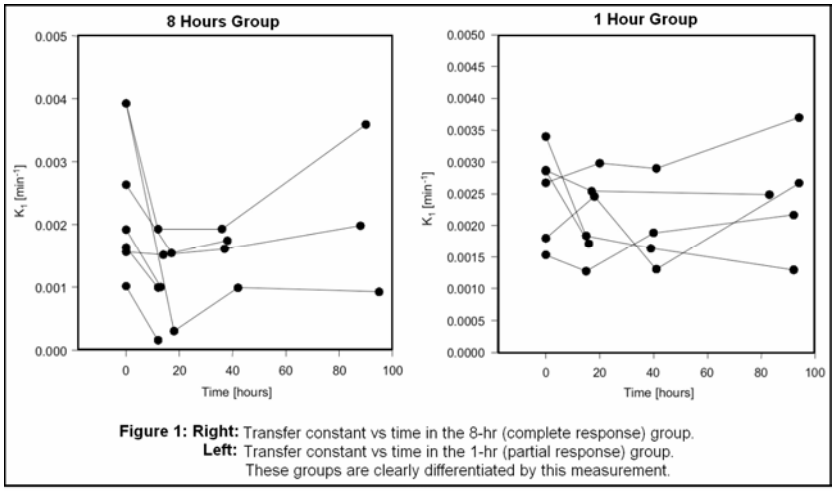

Figure 1: Right: Transfer constant vs time in the 8-hr (complete response) group. **Left:** Transfer constant vs time in the 1-hr (partial response) group. These groups are clearly differentiated by this measurement.

Using TOMROP image sets, pixel-by-pixel R1 maps (R1 = 1/T1) were constructed using a Maximum-Likelihood procedure constrained to yield non-negative estimates of the model parameters. The parameter ΔR1 in the tissue (ΔR1 = $R1_{post}$-$R1_{pre}$, where $R1_{post}$ is post-contrast, and $R1_{pre}$ is pre-contrast) was used as a measure of CA concentration in the tissue. ΔR1 in the sagittal sinus is taken as an estimate of CA arterial concentration. Using concentration-time records of CA concentration, with pixel-by-pixel estimates of ΔR1 on hand, and using the concentration-time techniques previously described (1), maps of the vascular transfer constant, K_1, were constructed. A region of interest (ROI) was manually selected by examination of the post-contrast high-resolution T1-weighted image, and the ROI's mean of the model 2 (Patlak model) estimate of K_1 was recorded.

Results: See Fig 1, in which K_1 in the tumor core is plotted versus time for the 8-hr group (left) and the 1-hr group. In the 8-hr group of animals, a uniform decrease appears at the first time point post-RT. Of the 7 studies available for this time point, 7 animals demonstrate a decrease in K_1 between the first and second study. When the differences between the control and first post-RT study (12 hrs) are evaluated, the 8 hr group shows a more than two-fold decrease in K_1 (from 2.3x10-3 to 1.1x10-3). The test-retest differences in even this small sample are significantly different from zero ($p < 0.05$), demonstrating that Cilengitide + RT acutely decreases the permeability of the vascular bed.

In the 1-hr group there were 6 studies available at the 12 hr point. In contrast to the 8-hr group, the change in K_1 is far less uniform. When the differences between the control and first post-RT study (12 hrs) are evaluated, the 1 hr group shows a small decrease in K_1 (from 2.5x10-3 to 2.1x10-3). The test-retest differences are not significant ($p > 0.1$). In 2 studies, K_1 increases at the 12 hour point, while it decreases in the other four. There also does not appear to be a uniform rebound at the 84 hr time point, possibly because the group decrease in permeability at the 12 hr point is not evident.

Discussion and Further Work: This ongoing study demonstrates the potential significance of the development of a validated measure of vascular permeability, in that it may be possible to develop a short-term evaluation of therapeutic intervention in malignant cerebral tumors that predicts the long-term outcome. This study's initial and very important conclusion is that permeability is probably a marker for the success of a therapeutic intervention.

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