

Diffusion MRI Early Prediction of Survival using Solvent Facilitated Perfusion of BCNU in a Rat Model of Glioma



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MOTIVATION

1. Solvent facilitated perfusion (SFP) after intratumoral (IT) injection is a promising therapy for glioma.
2. The need exists for non-invasive and clinically translatable means to reliably and rapidly assess different solvent types.
3. Diffusion MRI (DMRI) can characterize early changes in cellularity in a responding tumor, allowing early prediction of efficacy.

AIMS

1. To compare efficacy of IT injection of BCNU in (i) ethanol (EtOH) and (ii) 50%EtOH/50%PEG400 in a 9L rat orthotopic model of glioma.
2. To use T2-weighted MRI to measure tumor growth response to the SFP therapies.
3. To use diffusion MRI measurement of the apparent diffusion coefficient (ADC) to characterize early response to the SFP therapies.

BACKGROUND

SFP TREATMENT OF GLIOMA

- High grade glioma remains one of the least treatable forms of cancer, with a median survival of 1 year after initial diagnosis.
- Solvent facilitated perfusion (SFP) is a promising new approach to local chemotherapeutic delivery by direct injection. It utilizes the high translational mobility of certain organic solvents in the aqueous phase, and their ability to cross cell membranes.
- In rats, direct injection of BCNU dissolved in EtOH (DTI-015), has shown 100 times greater BCNU concentration in tumor than normal tissue, and increased efficacy and survival compared with systemic injection [1-4].

STUDY DESIGN

- Male Fisher 344 rats were injected into the right forebrain with 9L glioma cells (150,000 in 10 microliters) at a depth of 1.75 mm.
- At 19 days post-tumor implantation, rats with tumor volumes between 15-65 mm³ were distributed into three groups:
 - Untreated Control (n=8)
 - 1mg BCNU in 50µl EtOH (n=16)
 - 1mg BCNU in 50µl 50%EtOH/50%PEG400 (n=16)
- Direct injection of BCNU in each solvent (0.5µl/min) was accomplished using a micro-injector mounted in a stereotaxic frame. Injection coordinates were verified using MRI.

ENDPOINTS

- T2-weighted fast spin-echo MRI was used to evaluate tumor growth.
- Early indication of tumor cell kill was evaluated by diffusion-MRI measurement of the apparent diffusion coefficient (ADC), which is sensitive to early changes in tissue cellularity.
- Survival was used as the primary endpoint.

REFERENCES

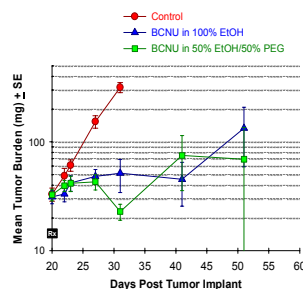
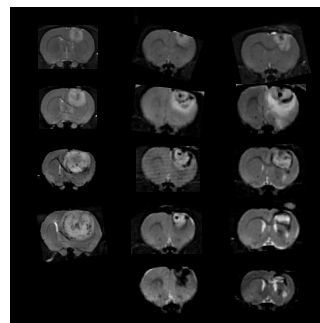
1. Hamstra, D.A., et al. J Neurooncol 2005;73:225-38.
2. Hall, D.E., et al. Clin Cancer Res 2004;10:7852-9.
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RESULTS AND CONCLUSIONS

Tumor Growth Response

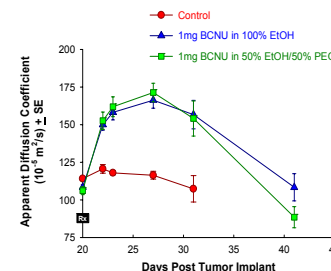
Untreated Control 1mg BCNU in 50µl EtOH 1mg BCNU in 50µl EtOH/PEG

Pre-Rx
1 Day Post-Rx
6 Days Post-Rx
10 Days Post-Rx
20 Days Post-Rx



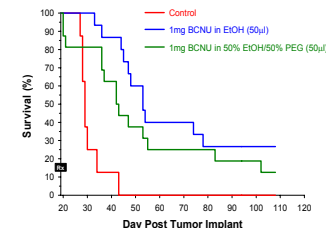
- ⇒ Both SFP therapies showed significant growth inhibition.
- ⇒ In each treated group there were 6/16 complete regressions, and 2/16 partial regressions.
- ⇒ There were 4 cures in the BCNU/EtOH treated group and 2 cures in the BCNU/EtOH/PEG group.

Early ADC Response



- ⇒ The untreated animals showed little change in ADC.
- ⇒ Both treated groups showed a robust early increase in ADC.
- ⇒ The ADC time courses through to peak ADC were indistinguishable between each SFP group.
- ⇒ ADC decreased 7 days after treatment in each group, with suggestion of a greater rate of decline in the BCNU/EtOH/PEG treated group.

Survival



- ⇒ Lifespan was significantly extended by both SFP therapies compared with untreated controls (EtOH: P<1e-6; EtOH/PEG: P=0.005).
- ⇒ The median survival difference between the EtOH group (53 days) and the EtOH/PEG group (43 days) was not statistically significant, however, there was a trend toward increased lifespan in the EtOH group.

Conclusions

- ⇒ SFP therapies for glioma represent a promising new strategy that may be further optimized in terms of solvent and/or cytotoxic agent choice.
- ⇒ Diffusion MRI (ADC) robustly predicted later tumor growth and survival, and is an efficient means for measuring SFP efficacy in orthotopic glioma.