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MOTIVATION

1. The Nestin tv-a mouse provides a promising model for glioma, driven by oncogenes of choice.
2. These models may provide a means for testing novel therapies, and an efficient way of optimizing new combination strategies.
3. Temozolomide is increasingly being used as the standard of care for human glioma.

AIMS

1. To use T2-weighted MRI to measure tv-a glioma growth response to Temozolomide.
2. To use diffusion MRI to measure tv-a glioma cellularity/cell kill response to Temozolomide.
3. To validate MRI methods in the Ntv-a model by correlation of tumor growth and ADC data with the survival endpoint.

BACKGROUND

THE Ntv-a TRANSGENIC

- The RCAS/tv-a transgenic system involves gene transfer through infection by the avian leucosis virus (ALV-A) in mice expressing the gene for the RCAS receptor (tv-a) [1].
- The nestin tv-a (Ntv-a) mouse, expresses tv-a under the control of the nestin promoter in glial-progenitors, and spontaneously develops glioma when infected with ALV-A that over-expresses PDGF [2].

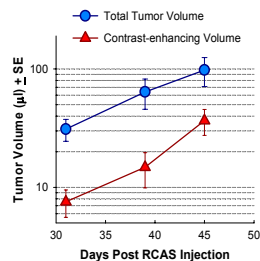
MODEL STAGING

- Ntv-a mice were injected into the brain with PDGF-encoding RCAS virus at birth.
- Ntv-a mice that had developed high grade gliomas were divided into 2 groups (vehicle control, n=12 and Temozolomide treated, 100mg/kg qdx5 ip, n=13).

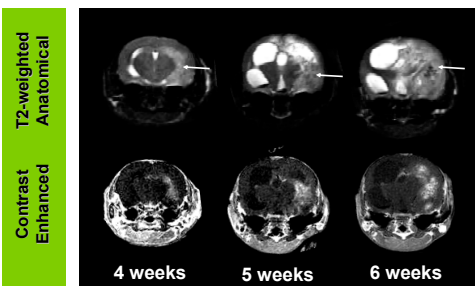
ENDPOINTS

- 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)**.
- **Survival** was used as the primary endpoint.

TV-A GLIOMA CHARACTERISTICS



⇒ MRI contrast enhancement indicates the vascular characteristics of high grade glioma.

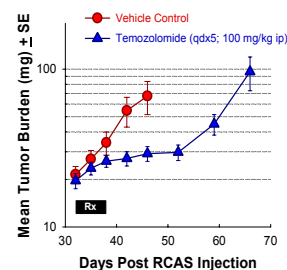


MODEL CHARACTERISTICS

- ⇒ aggressive tumor growth and vascular development.
- ⇒ median survival of 7.5 weeks.
- ⇒ MRI contrast-enhancement.
- ⇒ high cellular density.

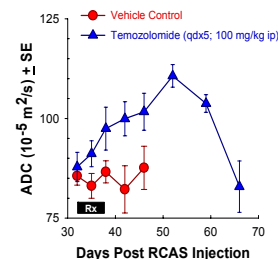
RESULTS AND CONCLUSIONS

Tumor Growth Response



⇒ temozolomide (100mg/kg qdx5 ip) treatment resulted in a growth delay of 14 days and net cell kill of 0.4 log units.

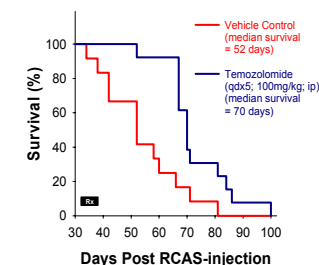
Early ADC Response



⇒ ADC showed an increase as early as 3-4 days into treatment, indicating tumor cell killing, and predicting gross effects in tumor growth and survival.

Survival

⇒ median survival in the control and treated groups was 52 and 70 days, respectively



Conclusions

- ⇒ MRI in the Ntva model is an efficient means for measuring efficacy.
- ⇒ MRI determined ADC increase and tumor growth response, were predictive of survival.
- ⇒ The ADC decrease was predictive of tumor regrowth.
- ⇒ This study highlights the potential use of ADC as a biomarker at both the preclinical and clinical levels.