Dynamic contrast-enhanced magnetic resonance perfusion weighted imaging (DCE-MRI) and diffusion weighted imaging (DWI) for pharmacodynamic evaluation of carboxyamidotriazole orotate (CTO) and temozolomide in malignant glioma

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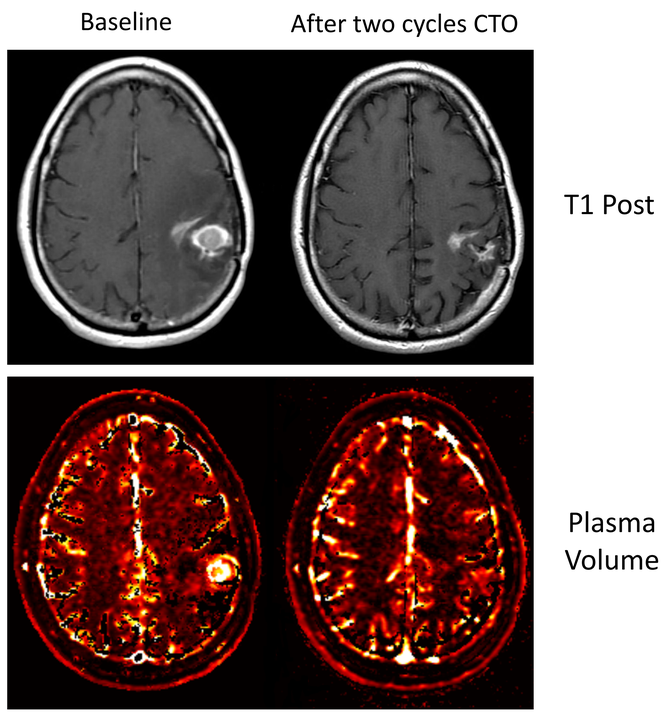
Background

- CTO is an oral inhibitor of non-voltage-dependent calcium signaling
- Modulates several pathways including EGFR, MEK, RAS, HDAC, HSP90, HSP90, WNT/B-catenin, Akt, ERK, VEGF, Bcr-Abl
- To determine *in human* pharmacodynamic effects of this drug , we evaluated advanced MRI parameters in an ongoing phase I trial of combined CTO and adjuvant temozolomide for recurrent malignant glioma

Methods

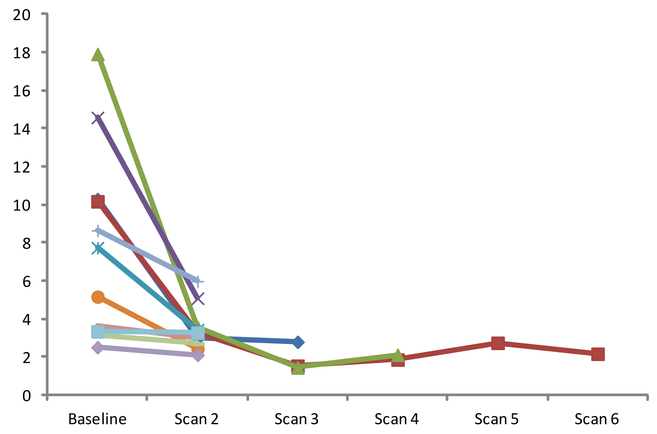
- Patients underwent DCE-MRI and DWI at baseline and after every two 28-day cycles
- Changes in imaging parameters were evaluated with volumetric histogram analysis of the tumor (NordiICEv2.3, Bergen, Norway)
- Assessed plasma volume (Vp), vascular permeability (Ktrans), and diffusion (ADC)
- Analyzed normalized results (tumor compared to normal brain tissue in each patient) with Mann-Whitney *u* tests

Example of Tumor Response with Decreased Perfusion in GBM

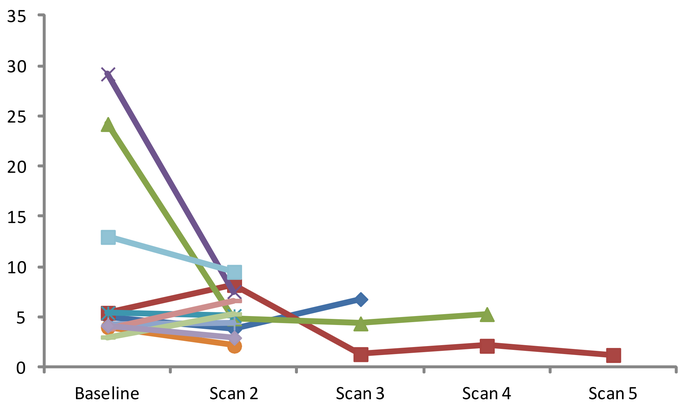


Change in parameters in all patients:

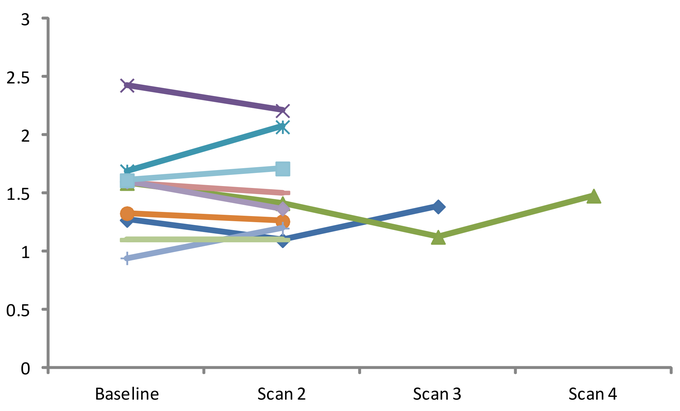
Plasma Volume



Permeability



Diffusion



Results- Patient Characteristics

- N=11 to date (9 Men, 2 Women)
- Histology: 9 GBM; 2 Grade III
- MGMT status:
  - 4 methylated
  - 4 unmethylated
  - 3 unknown
- Prior treatment:
  - All patients had prior surgery, RT, and TMZ
  - 3 Bevacizumab failures
- CTO dose range 219-812.5 mg/m^2/day
- Includes 2 pts with radiographic response on standard MRI.

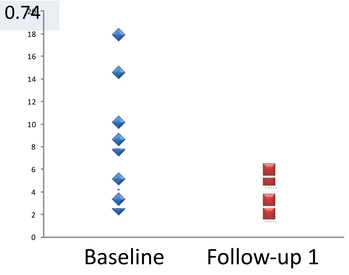
Results- Imaging Parameters

Baseline vs Initial Follow-up (after two cycles of CTO)

	Baseline mean	Follow-up mean	*P* value
Plasma Volume	7.93	3.45	**0.01**
Permeability	9.22	3.49	0.75
Diffusion	1.52	1.50	0.74

* All values are normalized and represent ratios of tumor to normal tissue

Plasma Volume



Conclusions

- Early Vp changes seen in all pts, providing proof-of-concept that non-voltage calcium channel blockade results in decreased blood perfusion in TMZ-refractory gliomas.
- Decreases in Vp were more apparent than in Ktrans, suggesting effects that are distinct from bevacizumab-induced VEGF blockade.
- Responders seemed to have higher baseline perfusion and permeability, requiring further investigation as potential biomarkers.
- Limitations: small number of pts, lack of perfusion in some scans.

➢ DCE-MRI is a useful tool to determine pharmacodynamic effects in early drug development.