

Early perfusion changes in patients with recurrent low-grade gliomas treated with everolimus (RAD001) under a phase II clinical trial

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Introduction

Low-grade gliomas (LGG) are slow-growing, primary brain tumors that frequently recur after primary surgical treatment. Recent work has established the activation of the PI3K/mTOR pathway in most LGG, raising the possibility that mTOR inhibitors such as everolimus (RAD001) may benefit patients with LGG [1]. Preclinical studies have shown that RAD001 has both antiproliferative and antiangiogenic effects on tissues with PI3K/mTOR activation [2,3]. Early imaging markers of treatment response and disease progression are needed to assess patients undergoing experimental therapy.

Methods

In this phase II clinical trial, 17 patients with recurrent low-grade gliomas were treated with everolimus. Serial multimodal magnetic resonance imaging was obtained every two months for up to 12 months while patients were undergoing treatment. At each time point, the volume of hyperintensity on T2-weighted imaging (T2ALL) and the contrast-enhancing lesion on T1-weighted imaging (CEL), if present, were manually defined. Maps of imaging parameters were generated, including the apparent diffusion coefficient (ADC) and fractional anisotropy (FA) from diffusion-weighted imaging, the fractional blood volume (fBV) and vascular permeability (K_{ps}) from dynamic contrast enhanced (DCE) perfusion-weighted imaging, and MR spectroscopic imaging derived parameters (peak heights of choline, lipid and lactate, and the choline to N-acetylaspartate index, CNI). Each parameter was normalized to its median value in normal-appearing white matter, and the median, 10th percentile and 90th percentile values were computed within the T2ALL and CEL volumes.

Results

At the time of analysis, five patients had experienced disease progression (range 3.2 to 15.8 months), 10 had stable disease (median follow-up 13.6 months) and two dropped out of the study due to adverse side effects. Thirteen patients did not experience progression during the first six months of treatment. Compared to baseline imaging parameters, these patients demonstrated a median decrease in the CEL volume of 94% at 4 months and 84% 6 months ($p=0.02$ and $p=0.04$ respectively, by Wilcoxon signed-rank test). In addition, patients not progressing during the first six months of treatment demonstrated a decrease in median fBV of 23% at 4 months ($p<0.001$) and 31% at 6 months ($p=0.001$). Similarly, the 90th percentile K_{ps} was decreased by 62% at 4 months ($p=0.04$) and 71% at 6 months ($p=0.02$). Spectroscopic and diffusion parameters did not change significantly for these subjects during the first 6 months of treatment.

Discussion

Everolimus, an mTOR inhibitor, has been shown to have both antiproliferative and antiangiogenic effects in preclinical studies [2,3]. In patients being treated with everolimus, we demonstrate significant alterations of tumor vascular properties, as measured by both the size of contrast-enhancing lesions and DCE perfusion-weighted MR, in the first six months of treatment. Specifically, we observe reductions both in fBV and K_{ps} , corresponding decreased capillary density and vascular permeability, respectively. To our knowledge, this is the first demonstration of antiangiogenic effects of an mTOR inhibitor in a clinical setting.

Conclusions

Patients with recurrent low-grade gliomas being treated with everolimus demonstrate significant alterations in tumor vascular properties, measurable by perfusion MRI, during the first six months of treatment. Perfusion parameters may thus represent an early marker of treatment response in these patients. More patients and longer follow-up are needed to determine whether the extent of these early treatment changes are predictive of treatment response and disease progression.

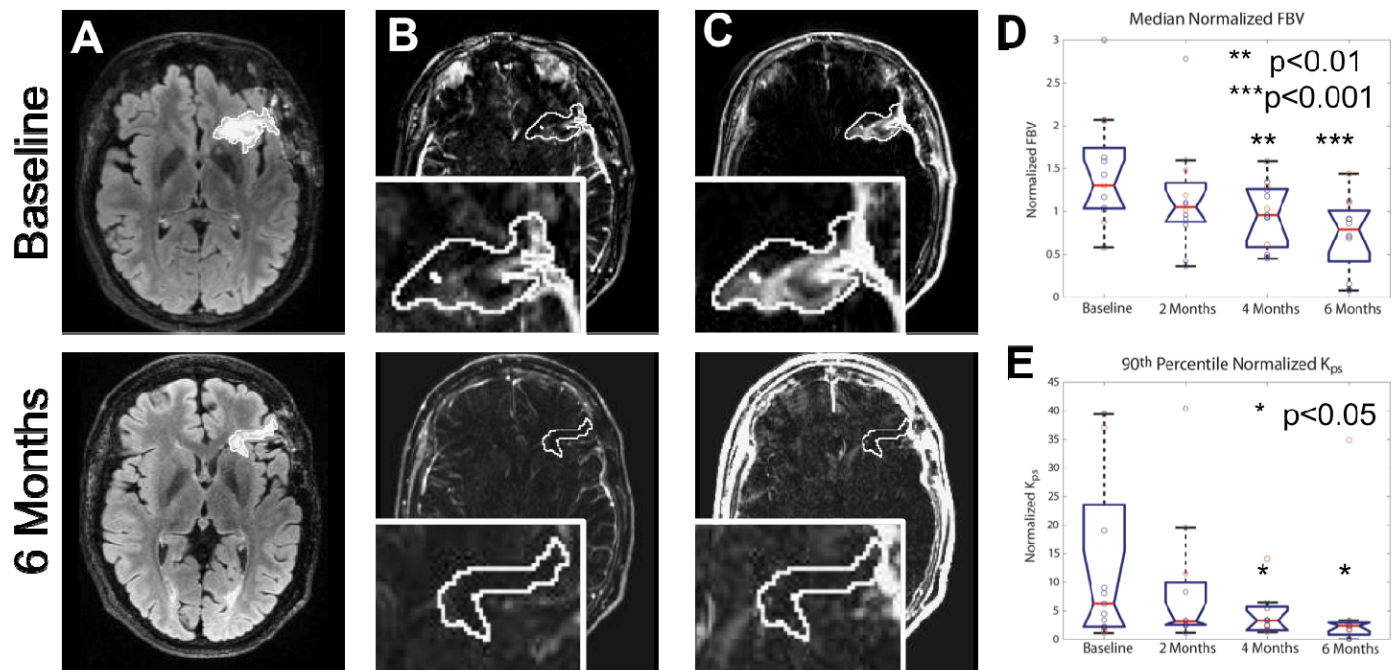


Figure 1. Example subject T2 FLAIR (A), fBV (B) and K_{ps} (C) images shown at start of treatment (top) and after six months of treatment (bottom). The T2ALL tumor region is expanded to demonstrate change in perfusion parameters after six months of treatment. (D) Median normalized fBV and (E) 90th percentile normalized K_{ps} in nonprogressors during first six months of treatment. Values significantly decreased from their baseline values are denoted with asterisks.

References and Acknowledgements: [1] McBride S et al. J Neurooncol 2010; 97: 33-40. [2] Hudson CC et al. Mol Cell Biol 2002; 22:7004-14. [3] Lane HA et al. Clin Cancer Res 2010; 15:1612-22. This study was supported by the UCSF Brain Tumor SPORC Grant P50 CA0972.