Using MR Spectroscopy to Track Metabolic Changes in Glioblastoma after One Dose of Cediranib

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INTRODUCTION

Proton magnetic resonance spectroscopy (^{1}H-MRS) is becoming a widely available tool for clinical studies of brain tumors patients. It provides information about the metabolic properties in regions of normal and abnormal tissue. This study investigated early changes in predominant metabolites for assessment of tumor response to anti-angiogenic agents in recurrent malignant glioblastoma (rGBM).

PATIENTS & METHODS

Thirty-one patients with rGBM treated with daily cycles of cediranib (45mg oral dose) were studied [1]. The patients were scanned using a 3T Siemens MRI scanner at different time points throughout the course of their treatment. In this study, we focused on early changes, one day after the treatment (Day 1). Chemical Shift Imaging, multi-voxel MRS, using a PRESS sequence with TR/TE/NS=1700ms/144ms/3 was used to acquire data from 16x16 voxels (1x1x1.4 cm^3). First and second order shimming was performed automatically, followed by a manual adjustment to optimize as necessary. MRI protocol also acquired including conventional sequences (i.e. T1, Fluid Attenuation Inversion Recovery (FLAIR), post-Gd T1, Apparent Diffusion Coefficient (ADC)) [1]. Spectroscopic raw data were processed using LC Model 6.1 software (Provencher, Ontario, CA). Using software written in Matlab, outputs were analyzed in two ROIs defined on the corresponding MRIs: enhancing tumor (ET) and normal tissue on the contralateral side (cNT). The changes in NAA and Cho on Day 1 were analyzed with respect to the values pre-treatmet (Day -1). The voxels with a SD>25% were excluded. The concentrations of the metabolites were normalized to the normal side creatine concentration (norCre). The changes in MRI parameters were analyzed in a similar way.

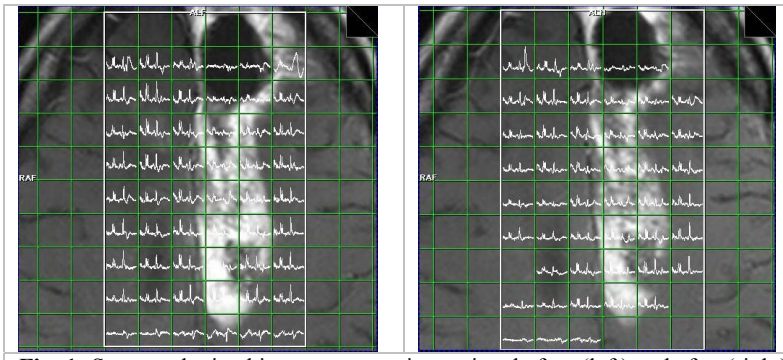

Fig. 1: Spectra obtained in a representative patient before (left) and after (right) one dose of cediranib.

RESULTS AND DISCUSSION

The spectra obtained from 19 out of 31 subjects were available for quantitative analysis based on data quality. The subjects were classified as either good or poor responders by their overall survival (OS) (longer than 6 months). **Fig. 1** shows MRIs and spectra on Day -1 and Day 1 for a representative patient.

After one dose (Day 1), NAA/norCre in ET showed a significant increase (26%, p=0.02) in good-OS patients (12/19) and no such increase in poor-OS. Interestingly, NAA/Cho, the most commonly used clinical criteria for discriminating normal and abnormal tissues, increased in good-OS patients but decreased in poor-OS. There were no significant changes in norCre or MRI parameters, including T1, FLAIR, and ADC. **Fig. 2** graphs the percent changes of metabolites after one dose (normalized by Day -1 values).

The significant change observed in NAA/norCre after one dose of cediranib is remarkable. If we assume that cediranib has an early cytotoxic effect, the metabolic changes are expected to be detected earlier (using 1H-MRS) than morphological changes. In this case, one interpretation of our data could be that neuronal activity is restored in the lesion (i.e. tumor cells are destroyed and displaced by normal cells). However, anti-angiogenic drugs have not been shown to have a cytotoxic effect on tumor after just one day. Therefore, the change in tumor metabolic profile is more likely explained by the partial volume effect and/or by the shifted volume of brain due to the reduction of tumor enhancement. This most probably results from a decrease of hydration level (i.e. vasogenic edema and ADC) because the concentrations of many metabolites vary with it. Even so, they were not large enough to have the significant effect demonstrated in **Fig. 2** and in our previous MRI study [1]. In particular, good- and poor-OS cases showed comparable changes of MRI parameters, but NAA/norCre values increased significantly only in good-OS. One interesting observation is that FLAIR slightly decreased in good-OS but increased in poor-OS even though it did not show a low p-value. This implies that FLAIR using T2 would be a more sensitive marker for detecting an edema than ADC and that ADC reflects several complicated effects, which is comparable to previous studies. [2] The changes in NAA/Cho (i.e. increase of NAA/Cho in good-OS and decrease in poor-OS) is also of interest as it has great potential as a biomarker that predicts response to an anti-angiogenic treatment.

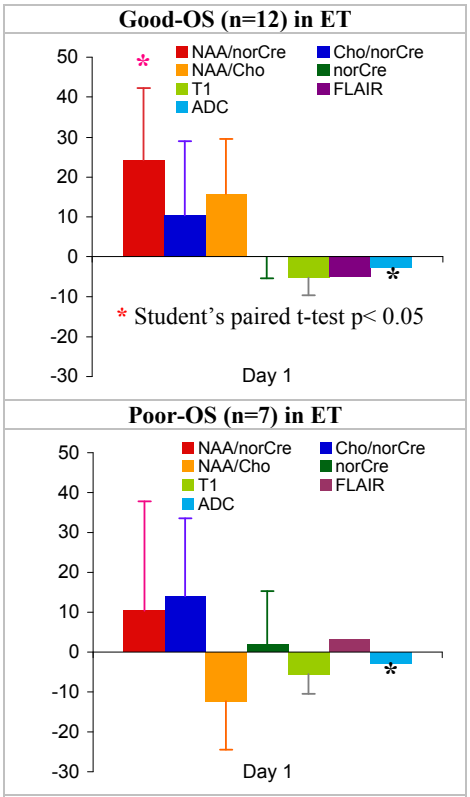

Fig. 2: MRS and MRI Changes in good overall survival (OS) (top) and poor-OS (bottom) after one dose relative to baseline. (* p<0.05)

CONCLUSION

This prospective study provides preliminary evidence that 1H-MRS could serve as a biomarker for predicting treatment responses in rGBM patients. The change in NAA/norCre in ET after one dose could suggest a revival of neuronal activity as well as a recovery of metabolite concentrations due to reduction of edema. NAA/Cho changes also seem to correlate well with overall survival. These observations have important implications for treatment management.

REFERENCES [1] Batchelor TT, Sorensen AG, Jain RK, Cancer Cell 11:83-95 (2007) [2] Nelson SJ et al, jMRM 21:701–708 (2005)