

Is Serial MR Spectroscopy Revealing an Anti-tumor Effect of Cediranib in Human Glioblastoma?

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INTRODUCTION

Proton magnetic resonance spectroscopy (¹H-MRS) is becoming a more widely available tool for clinical studies of patients with brain tumors, providing information about the metabolic properties in regions of normal and abnormal tissue morphology. In this study, the changes in predominant metabolites were evaluated for providing supplementary information in the assessment of the response of cancerous tissue to anti-angiogenic agents in patients with recurrent malignant glioblastoma (rGBM), in addition to the high-quality anatomical data provided by conventional MR imaging techniques.

PATIENTS & METHODS

Thirty-one patients with rGBM treated with daily cycles of cediranib, a potent oral, pan-VGEF receptor tyrosine kinase inhibitor treatment (45mg daily by mouth), were studied [1]. The patients were scanned using a 3T Siemens MRI scanner at different time points in the course of their treatment: 3-7 days and 1day before the treatment, and 1day, 26-28 days, 54-56 days, 110-112 days and 166-168 days after treatment. CSI, multi-voxel MRS using a PRESS sequence for water suppression and a weighted k-space sampling with TR/TE/NS=1700/135 or 144/3 ms was used to acquire data from 16x16 voxels, each measuring 1x1x1.4 cm³. The first and second order shimming was performed automatically, followed by a manual adjustment if necessary. Spectroscopic raw data were processed using the LC Model 6.1 software (Provencher, Ontario, CA). The LC Model output values were analyzed using software written in Matlab in two ROIs defined on the corresponding MRIs: (1) enhancing tumor (ET), and (2) normal tissue on the contralateral side of tumor (cNT). The changes in two metabolites, NAA and Cho, were studied. The voxels with a SD>25% were excluded and the concentrations of the metabolites were normalized to the normal side creatine concentration (norCre).

RESULTS AND DISCUSSION

The spectra obtained from 20 out of 31 subjects were available for quantitative analysis. Based on their overall survival (OS) (longer than 150 days), the subjects were classified into either good or poor responders.

After one dose (Day 1), NAA/norCre in ET showed a significant increase (26%, p=0.02 in good OS patients (13/19). At day 28, both NAA/norCre and Cho/norCre in ET showed significant increases in all 20 patients (38% and 37%, respectively, p<0.05); NAA/norCre increased with 38% (p<0.05) and Cho/norCre increased with 36% in the good OS patients. At day 56, NAA/norCre continued to increase (60%, p<0.05) in all the subjects, while the Cho/norCre started to decrease, although its level was still higher than the baseline (8%). In the cNT regions there was no significant change of both NAA/norCre and Cho/norCre throughout all visits. The graphs for the NAA/norCre and Cho/norCre for their early changes (day 1, 28, and 56) from day -1 are shown in Fig.1. MRIs and spectra for two early time points, one day before/after the treatment for a representative patient are shown in Fig. 2.

The changes observed in NAA/norCre and Cho/norCre concentrations after one dose of cediranib are quite intriguing. On one hand, assuming that cediranib has indeed an early cytotoxic effect, the metabolic changes are expected to be detected using ¹H-MRS earlier than the morphological changes using conventional MRI. In this case, one interpretation of our data could be that there is a cell recovery process in the region (i.e. tumor cells are destroyed and displaced by normal cells). On the other hand, the change in the tumor metabolic profile could also be explained by the reduction of vasogenic edema in the region. The concentrations of various metabolites (e.g. Cho, Cre, myoI) have been previously shown to vary with the hydration level. This osmotic effect is however less likely to be the explanation for the changes observed at Day 28 (NAA/norCre and Cho/norCre measured in all 20 patients showed significant changes at this time point).

CONCLUSION

By evaluating the early changes in the predominant metabolites, an anti-tumor effect of cediranib could potentially be detected. In spite of the biological and technical challenges involved in analyzing in-vivo tumor spectra (i.e. small signal-to-noise ratio, inefficient water suppression due to the short T2 of the tumor, presence of necrosis), ¹H-MRS is a very promising method adjunct to anatomical imaging, which could provide valuable information for assessing the early response of cancerous tissue to anti-angiogenic treatment in recurrent glioblastoma.

REFERENCES

[1] T.T. Batchelor, A.G. Sorensen, R.K. Jain, Cancer Cell 11, 83-95, Jan. 2007

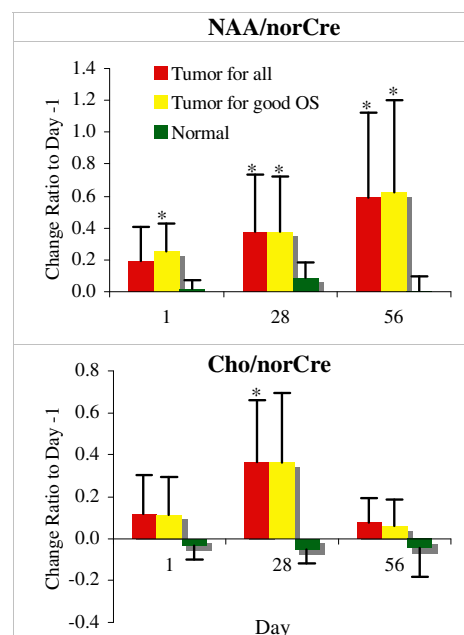


Fig. 1: Changes in normalized NAA (top) and Cho (bottom) at early time points relative to baseline. (* p<0.05)

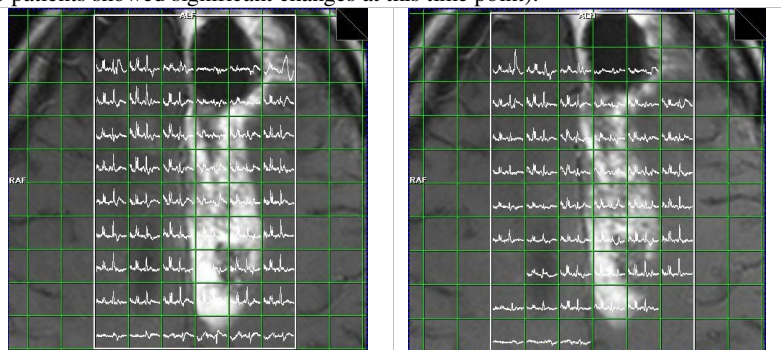


Fig. 2: Spectra obtained in a representative patient before (left) and after (right) one dose of cediranib.