1H-MR Spectroscopy as a Cancer Biomarker for Anti-angiogenic Treatment in Glioblastoma

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INTRODUCTION: A previous study of 31 glioblastoma multiforme (GBM) patients enrolled in a phase 2 clinical trial of the anti-angiogenic agent AZD2171 - a pan-VEGF receptor tyrosine kinase inhibitor - demonstrated the efficiency of this treatment using MRI markers such as tumor enhancement, blood vessel size, blood-brain barrier permeability, edema, water diffusion and tumor mass effect. However, there is a concern that the changes observed using standard MR imaging do not directly relate to tumor cell changes. A recent study of brain tumors in pediatric patients has suggested that the information obtained by proton MR spectroscopy (^{1}H-MRS) is independent of that obtained from MRI. ^{1}H-MRS could provide additional information regarding the response of cancerous tissue to the anti-angiogenic treatment.

PATIENTS & METHODS: Chemical Shift Imaging (CSI) data were analyzed for 20 patients (mean age 53.7, range 20-77) with recurrent GBM. The patients were scanned using a 3T MRI scanner (TimTrio, Siemens, Malvern, PA) 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 (visits 1 through 7) after the AZD2171 treatment (45mg daily by mouth). Based on the tumor responses on standard MRI (e.g. contrast enhancement, vessel size, peritumoral edema) up to 28 days, the patients were categorized into good (16 out of 20) and poor responding (4 out of 20). A PRESS (point resolved spectroscopy) sequence using weighted k-space sampling with TR/TE/NS=1700/135 or 144/3 ms was used to acquire the data from 16x16 voxels, each measuring 1x1x1.4 cm^3. The first and second order shimming was performed automatically and it was followed by a manual adjustment if necessary. LC Model 6.1 software (Provencher, Ontario, CA) was used to analyze the raw data in three regions of interest (ROIs) defined on the corresponding MRIs: (1) enhancing tumor (ET), (2) non-enhancing surrounding tumor (peritumoral tissue) (PT), and (3) normal tissue on the contralateral side of tumor (cNT). The LC Model output values were analyzed using software written in Matlab. The changes in the metabolites N-acetyl aspartate (NAA), choline (Cho) and lactate (Lac) were studied. The voxels with a standard deviation higher than 25% were excluded and the concentrations of all metabolites were normalized to the normal side creatine concentration (norCr).

RESULTS AND DISCUSSION: The NAA/Cho in the ET region showed no significant change during 1-28 days. In most cases (14 out of 16), it increased rapidly between day 28-56 days and reached a maximum around day 56-112 days. The percentage change was in the 50-100 % range. In all the patients, NAA/Cho decreased at 112-168 days. No significant change was observed during the treatment in the PT regions. There were small fluctuations (5-10%) and a large decrease at the final scan in 14 out of 16 patients. The other two patients having no big change in the ET showed a 20-30 % increase in the PT. In the cNT regions NAA/Cho was constant. The number of voxels having a NAA/Cho greater than 5 (characteristic of normal tissue) increased during the study.

In all poor-responding patients no significant changes were observed in any of the three regions until day 28, the trend being very similar to the one observed for the good-responding patients. This implies that MRS supplements the information provided by MRI. The MRIs for all the visits, the colormaps and a graph for the NAA/Cho for a representative patient are shown in **Fig. 1a-c**.

In the ET regions, Lac/norCr generally decreases during the treatment, which probably indicates a decrease in the tumor cell hypoxia.

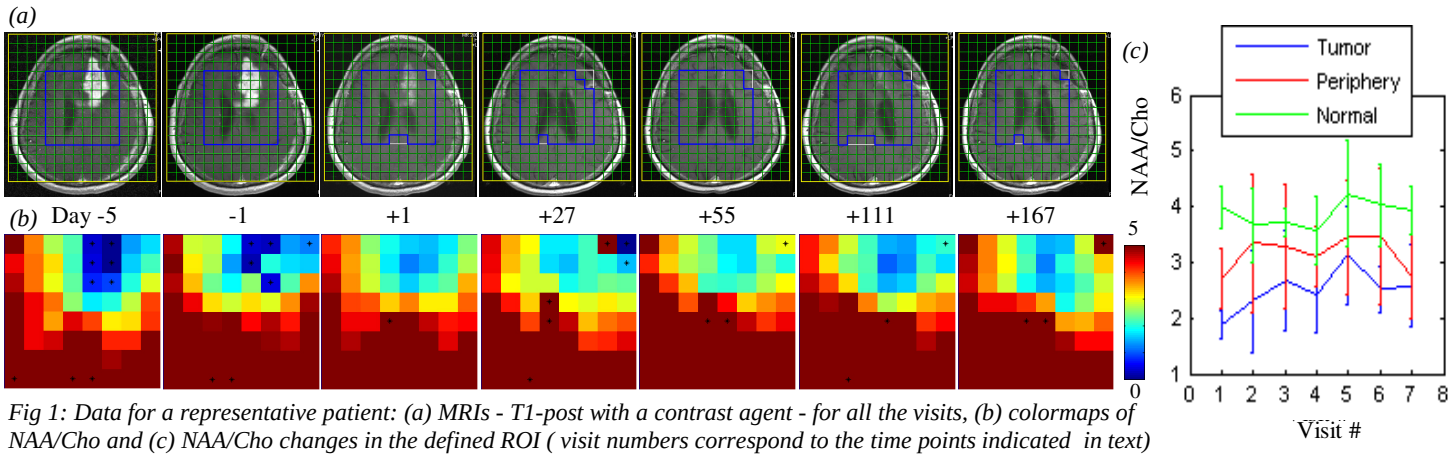

Fig 1: Data for a representative patient: (a) MRIs - T1-post with a contrast agent - for all the visits, (b) colormaps of NAA/Cho and (c) NAA/Cho changes in the defined ROI (visit numbers correspond to the time points indicated in text)

CONCLUSION: The NAA/Cho measured in twenty patients showed no significant changes until day 28 and decreased afterwards. The tumor is likely to regress after 28-56 days, later than the enhancement changes on the MRI. This suggests that the regression of the tumor follows its vascular breakdown by the anti-angiogenic agent and the recovery of its angiogenic balance may result in its recurrence. Assessing the therapeutic effect in the peritumoral region is very difficult at this spatial resolution. This tissue could escape the antiangiogenic effect as it derives its blood and nutrient supply from the surrounding normal tissue, but partial volume effects could easily confound our findings. We speculate that one interpretation of our data is that signs of tumor regression appear later, while those of tumor recurrence earlier on 1H-MRS than on MRI.

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), ^{1}H-MRS is a very promising method, which could provide valuable information for assessing the response of cancerous tissue to anti-angiogenic treatment.

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