Diffusion Tensor Imaging in Assessing Anti-angiogenic Treatment in Glioblastoma

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Introduction: Glioblastoma multiforme (GBM) is characterized by rapid growth and aggressive infiltration to and propagation along the white matter tracts. In addition, vasogenic edema usually occurs due to the abnormally tortuous and leaky tumor vasculature. Diffusion tensor imaging (DTI) provides an opportunity to measure the magnitude and directionality of the water diffusion. Additionally, white matter tractography can be generated [1] and this may suggest directions of future tumor spread. In the current study, DTI was used to assess the treatment effect of an anti-angiogenic agent AZD2171, a pan-VGEF receptor tyrosine kinase inhibitor, in a phase-II clinical trial (AstraZeneca; ClinicalTrials.gov identifier: NCT00254943)

Patients and methods: Nineteen consecutive patients (mean age 55.6, range 24-77 years) with recurrent GBM underwent repetitive MRI with Auto-Align technique [2] in the same 3T MRI scanner (TimTrio, Siemens Medical Solutions, Malvern, PA) 3-7 days before, 1 day before, 1 day, 26-28 days, 54-56 days, 110-112 days after AZD2171 treatment (45 mg daily by mouth) started. Sixty slices of twice-refocused echo-planar diffusion-weighted images were acquired with TR 7500 ms, TE 84 ms and a b-value of 700 s/mm2 in 42 directions as well as 7 low b value images to allow reconstruction of the diffusion tensor at each voxel. Resolution was 2 mm isotropic, with a 128x128 matrix. Standard T2-TSE, FLAIR, pre- and post-contrast T1 images were also acquired at each visit. Apparent diffusion coefficient (ADC) and fractional anisotropy (FA) maps were created from the low and high b value images using custom-written software implementing the standard algorithm, and 3D white matter tracts were reconstructed. The maps and the tracts of all other visits were co-registered to day-1 and four regions of interest (ROIs) of this visit were outlined by a blinded neuroradiologist (**Fig. 1**): (1) enhancing tumor (ET); (2) non-enhancing peritumoral edematous brain (NPEB) defined on FLAIR images; (3) normal appearing white matter adjacent to but separate from the high ADC/high T2 signal edematous brain (aNAWM), 120-150 voxels were manually selected in multiple slices; and (4) normal appearing white matter in corresponding regions on the contralateral side (cNAWM). Mean ADC, mean FA values of each ROI, and the number of white matter tracts which crossed each ROI, were calculated and compared to day-1 visit with paired *t*-test. P<0.05 was considered statistically significant.

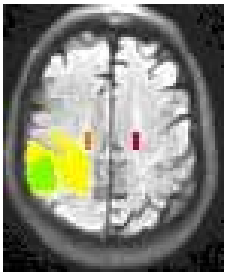

Fig.1. FLAIR image showing four ROIs. Green: ET; Yellow: NPEB Orange: aNAWM; Red:cNAWM.

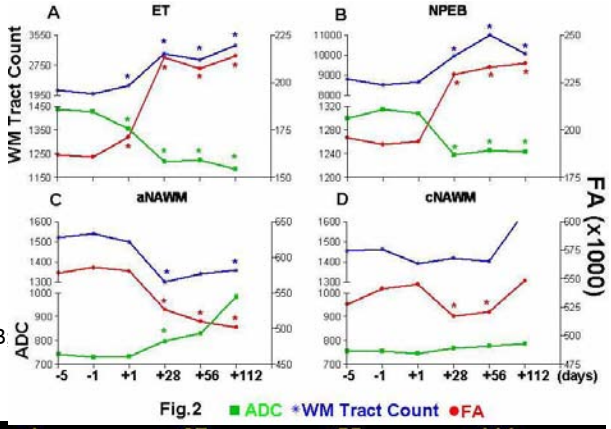

Fig.2 ■ ADC *WM Tract Count ●FA

Results and discussion: In ET response to anti-angiogenic treatment was immediate: ADC decreased, FA and the number of tracts increased after a single dose on day1, and continued so on day28, 56, and 112 (**Fig. 2A**). This indicates that vasogenic edema was reduced and that displaced white matter tracts were returning to their original positions. In NPEB the same significant changes of ADC, FA, and the number of tracts were also detected, though in a delayed mode until day28, 56 and 112(**Fig. 2B**). In aNAWM, however, ADC increased on day28, FA decreased on day28, 56, and 112, and the number of tracts decreased on day28 and day112, possibly suggesting the outward breakthrough of the tumor (**Fig. 2C**). In cNAWM (**Fig. 2D**) the fluctuation of FA values was significant, but whether AZD2171 has general effect in cerebral water diffusion remains unclear. Out of 18 patients who had both day-1 and day28 DTI, 15 patients' FA and 10 patients'ADC fulfilled this pattern of increased ADC and decreased FA around the tumor while simultaneously decreased ADC and increased FA in the tumor, a pattern suggesting central anti-tumor effect but peripheral tumor spread. A representative patient's DTI is shown in **Fig. 3.**

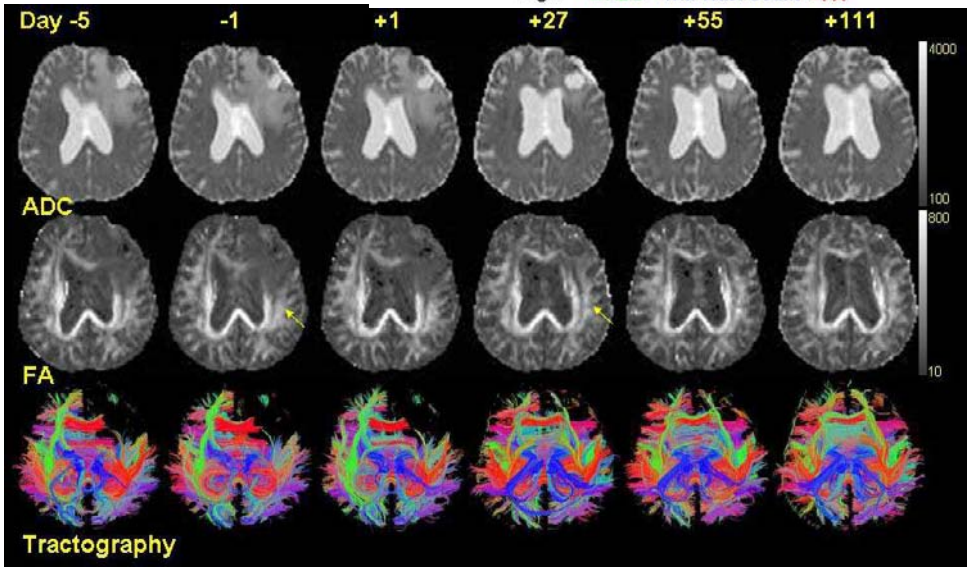

Fig. 3. A representative patient showing the ADC, FA (scaled by 1000), and tract changes after anti-angiogenic treatment. Arrows indicate the subtle decrease of FA in aNAWM on day+27 compared to day-1. Tractography was masked by FA and B0 maps.

Conclusions: The enhancing tumor was most sensitive to the anti-angiogenic agent, AZD2171, and non-enhancing peritumoral edema was less sensitive although there was evidence of treatment effect by 4 weeks. Our data also suggested that monotherapy of AZD2171 was not potent enough to prevent the tumor infiltration in adjacent NAWM. DTI is a valuable biomarker to assess the brain tumor treatment and to investigate underlying treatment mechanisms and effects.

References:

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