Assessment of Anti-angiogenic Treatment in Glioblastoma using Arterial Spin-Labeling and Dynamic Susceptibility Contrast Perfusion MRI in a Phase II Trial

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Introduction: Angiogenesis is an essential step in the growth and spread of solid tumor, and advances in MRI now permit detection of the hemodynamic changes of glioblastoma after treatment [1]. In the current study, arterial spin-labeling (ASL) and first-pass dynamic susceptibility contrast (DSC) perfusion MRI were used to assess the treatment effect of an anti-angiogenic agent AZD2171, a pan-VEGF receptor tyrosine kinase inhibitor, in a phase-II clinical trial (AstraZeneca; ClinicalTrials.gov identifier: NCT00254943).

Patients and Methods: Twenty-nine consecutive patients (mean age 54.7, range 24-77 years) with recurrent glioblastoma 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. A pulsed ASL in the multisection mode, the second version of quantitative imaging of perfusion by using a single subtraction with addition of thin-section periodic saturation after inversion and a time delay (Q2TIPS), was used to create 6 slices relative cerebral blood flow (rCBF) maps. A 75 mm slab of tissue was imaged using a dual-echo, combined gradient-echo, and spin-echo echo planar DSC perfusion MRI (Gd-DTPA, 0.2 mmol/kg, 5ml/s) to enable rCBF, relative cerebral blood volume (rCBV) and relaive vessel size mapping [3]. Enhancing lesions were outlined using manual tracing Alice software on post-contrast magnetization prepared rapid gradient echo (MPRAGE). The outlines were coregistered to the perfusion maps of ASL and DSC and median values across the entire enhancing lesion and contralateral hemisphere without cerebral spin fluid were computed. The mean ratios of perfusion values of tumor to contralateral hemisphere (rCBF/Brain, rCBV/Brain, rVesselSize/Brain) at each visit were calculated and compared to day-1 visit with paired t-test. The correlation between ASL and DSC rCBF/Brain values and percent change of rCBFs and volumes across 1 day, 28 days and 56 days were analyzed as well. P < 0.05 was considered statistically significant.

Results and discussion: Compared with values at day-1, rCBF/Brain of ASL decreased significantly as early as 1 day after the onset of AZD2171 treatment and reversed a little at day 28. At day 112, it reversed significantly toward abnormal values (Fig. 1). Both rCBF/Brain and rCBV/Brain of DSC also decreased at day1 but started the reversal at day 28 and continued so at day 56 and 112 (Fig. 1). The same significant reduction was also detected in rVesselSize/Brain at day 1 and the reduction continued at day 28. At day 56, the rVesselSize/Brain reversed toward abnormal values, suggesting the beginning of the closure of the structural vascular normalization window (Fig. 1). A representative patient’s ASL and DSC are shown in Fig. 2. There was a moderate correlation between ASL and DSC rCBF/Brain in 133 scans (r = 0.61, 95% Cl: 0.50-0.71, p < 0.0001). However, no correlations were found between percent change of ASL or DSC rCBFs and percent change of tumor volumes across 1 day, 28 and 56 days (p > 0.05).

Conclusions: Both ASL and DSC can detect the rCBF changes of tumors after anti-angiogenesis treatment, but the limited signal-to-noise ratio of ASL may weaken its statistical power. DSC can also provide more valuable information about tumor rCBV and vessel size changes after treatment. The changes of tumor perfusion values of both ASL and DSC after AZD2171 treatment support tumor vascular normalization and reversal, which may allow development of patient-specific therapy to improve outcome in patients with glioblastoma.

References:

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