DCE-MRI of genetic mouse model of lung cancer

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Introduction

Antiangiogenic therapies for cancer that block vascular endothelial growth factor (VEGF) signaling have been shown to reduce both perfusion and permeability of the vasculature in tumors, with DCE-MRI proving to be an outstanding pharmacodynamic marker for therapies that target the VEGF axis [1]. Treatment with an antibody to VEGF-A has been shown effective in reducing tumor growth and extending survival in a genetic mouse model of lung cancer [2].Our goal was to evaluate the vascular effects of anti-VEGF-A antibody treatment in this model with DCE-MRI. Small (Gd-DTPA) and intermediate (Gadomer 17) molecular weight contrast agents were used in two separate studies using the same imaging protocol. Gadomer 17 has been proposed as a sensitive alternative contrast agent for detecting antiangiogenic treatment effect in tumors because of larger size [3]. Respiratory motion and the relatively small size of lung tumors present major challenges for the imaging. To overcome this we employed a respiratory-gated DCE-MRI protocol. To our knowledge, DCE-MRI in a genetic mouse model of lung cancer has not been reported previously.

Methods

Genetically Engineered Mouse Model (GEMM) of Non-small Cell Lung Cancer (NSCLC) [2]: K-ras.G12D.LoxP; p53.Cond.Frt conditional mice were infected with Adenoviral-FLPe/IRES/Cre that triggers the development of carcinomas in the lung. The mice were enrolled to the MRI study based on in vivo micro-CT (Scanco Medical, VivaCT 40 and 75) estimates of tumor burden. MRI was performed on a 9.4T Varian MRI system using a 35 mm quadrature volume coil. DCE-MRI employed a variable flip angle technique [4] using a 3D spoiled gradient echo sequence. TR=6 ms, TE=1.25 ms. Flip angles 2 and 10 degrees. NA=4. Contrast agent was administered via a tail vein catheter and postcontrast images were acquired for 30 min at 10 degrees flip angle, NA=1. 64×64×32 matrix, 30 mm × 30 mm × 32 mm FOV. During each expiration period, 10 dummy excitations were followed by 64 1st PE acquisitions. Temporal resolution was 32 * respiration period, typically 30 sec. Mice were treated on Day 0 with either anti-VEGF or control antibody (Gd-DTPA study: n = 12 and 14; Gadomer 17 study: n = 10 and 8, respectively), 5 mg/kg twice a week, and imaged on Day 0 (baseline), and Day 2 (post-treatment). On Day 15 the mice were re-imaged on micro-CT to assess tumor growth.

Pre- and postcontrast R1 maps were generated from the data to get estimates of contrast agent concentration in tissue (C_t): $R_1 - R_{10} = r_1 C_t$. Standard 2-compartment kinetic model [5] was used to calculate volume transfer constant (K^{trans}), fractional plasma volume (v_p), and fractional extra-vascular, extra-cellular space (v_e) for each voxel. The fitting was evaluated using 10 or 30 min of the postcontrast data: 10 min mostly provided a better fit and was used for this analysis. Initial Area Under Curve at 180 sec (IAUC180), was also calculated. Standard arterial input functions were used for both contrast agents. Mean K^{trans} and IAUC180 were calculated within manually drawn ROIs for each tumor and the per cent change from Day 0 to Day 2 was calculated. A mixed-effects model was used in statistical analysis to estimate the significance of the treatment effect. Within sample coefficient of variation (wCV) was estimated within the control group from Day 0 to Day 2.

Results and Discussion

As expected, the mean K^{trans} of all tumors at baseline was higher for Gd-DTPA than Gadomer 17 (Table 1), likely due to its smaller size. The variability in K^{trans} with both contrast agents was acceptable (Table 1) and comparable to published values in clinical studies [6]. With Gadomer 17, a significant decrease was observed in both K^{trans} (mean ± SEM: -45±8% vs. 7±9%, $p<0.001$) and IAUC180 (-29±5% vs. 4±6%, $p<0.001$) in the anti-VEGF treated mice compared to control (Fig. 1,2). When Gd-DTPA was used, the change in K^{trans} (-13±6% vs. -6±6%, $p=0.46$) and IAUC180 (-5±3 % vs. 3±3 %, $p=0.07$) was not statistically different from control. In both studies, the IAUC180 parameter had smaller wCV than K^{trans} (Table 1), but the relative change due to treatment was greater in K^{trans} than IAUC180 with Gadomer 17. No significant differences were observed in v_p or v_e. Gadomer 17 was found to be more suitable for DCE-MRI in this mouse model of lung cancer. Gadomer 17 benefits from slower extravasation, which can make it more sensitive to changes in permeability and less susceptible to error when temporal resolution is compromised by the respiratory gating [7].

Table 1.

	Baseline Ktrans mean ± SD (1/min)	wCV in Ktrans	wCV in IAUC180
Gd-DTPA	0.086 ± 0.026	21%	10%
Gadomer 17	0.040 ± 0.020	25%	17%

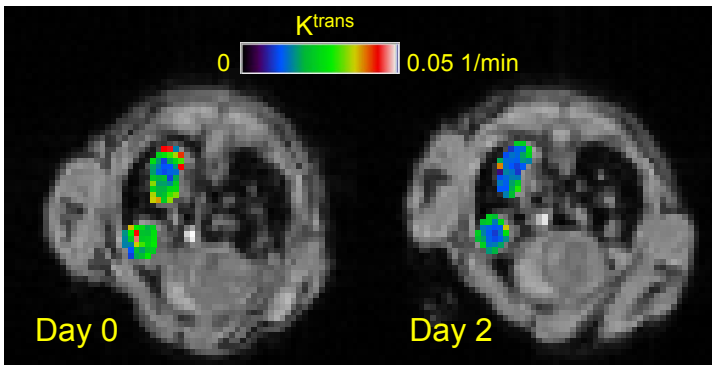

Figure 1. K^{trans} maps acquired with Gadomer 17 within two lung tumors overlaid on anatomical reference image before and after anti-VEGF antibody treatment.

References

[1] O'Connor, et al. Br J Cancer, 96: 189-195, 2007.
[2] Singh M, et al. Nat Biotechnol. 2010 Jun;28(6):585-93.
[3] Turetschek K, J Magn Reson Imaging. 2004 Jul;20(1):138-44.
[4] Brookes JA et al. Br J Radiol 1996;69:206–214.
[5] Tofts PS, et al. J Magn Reson Imaging 1997;7:91–101.
[6] Ng CS, et al. AJR 2010; 194:W134–W140
[7] Jaspers K, et al. MRM 2009; 62:779–787.

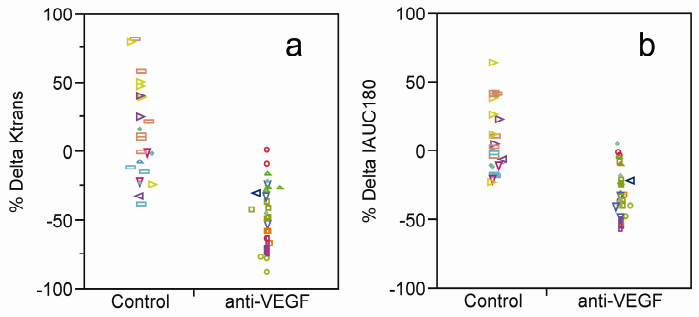

Figure 2. Per cent change in K^{trans} (a) and IAUC180 (b) with Gadomer 17 for each tumor. The tumors for each animal are shown with the same symbol.