**DCE-MRI evaluation of the temporal effects of bevacizumab-induced anti-vascular effects in colorectal cancer liver metastases**

J. P. O'Connor, 1, C. G. Jayson, 2, A. Jackson, 1, C. J. Rose, 1, C. L. Mitchell, 1, Y. Watson, 1, C. Roberts, 1, S. Cheung, 1, G. A. Buonaccorsi, 1, A. R. Clamp, 1, J. Hasan, 1, L. Hope, 1, K. Davies, 3, O. del Puerto, 1, and G. J. Parker 1

1Imaging Science & Biomedical Engineering, University of Manchester, Manchester, United Kingdom. 2Medical Oncology, Christie Hospital, Manchester, United Kingdom, and 3Roche Products Ltd, Welwyn Garden City, United Kingdom

**Introduction**

Vascular endothelial growth factor (VEGF) plays a crucial role in angiogenesis, enabling tumour growth and survival. Inhibition of VEGF signaling has become an important target in drug development, leading to FDA approval of drugs that target either VEGF or the VEGF receptor (VEGFR). In particular, phase III trials of the humanized anti-VEGF antibody bevacizumab (Avastin; Genentech, San Francisco, CA) in combination with cytotoxic chemotherapeutics have shown improved overall survival in patients with metastatic colorectal cancer. Dynamic contrast-enhanced imaging has been widely used in phase III trials of VEGF inhibitors, to produce pharmacodynamic biomarkers of drug efficacy. However, no detailed imaging studies have been performed to evaluate the magnitude, duration and temporal changes of anti-vascular effects, which may prove useful to comprehensively determine the sequence, magnitude and duration of anti-vascular effects induced by bevacizumab in a study of patients with colorectal cancer liver metastases evaluated using MRI.

**Patient recruitment**

Ethical approval was obtained from the Local Research Ethics Committee. Ten patients with liver metastases, with no previous treatment, were recruited in an open label study. Patients with history proven epithelial colorectal carcinoma, aged ≥18 years with an Eastern Cooperative Oncology Group score between 0-2, and life expectancy of at least 3 months were eligible. Written informed consent was obtained. Patients received single agent 10 mg/kg bevacizumab over a two week cycle. MRI scans were performed twice at baseline to establish parameter repeatability and at 4 and 48 hours post-treatment and on days 8 and 12.

**Image acquisition**

Data were acquired on a 1.5 tesla Philips Intera system (Philips Medical Systems, Best, Netherlands). After initial anatomical T1- and T2-weighted images, DCE-MRI was performed. 3D axial T1-weighted FFE volumes were consecutively-acquired (TR 4.5 ms, TE 2.9 ms, flip angle 10°, 405 3 mm slices, matrix 128 x 128, 25 slices with slice thickness 4 mm) following calculation baseline of T1 (t = 2*10^2/200; 4 signal averages; identical TR, TE, imaging matrix and slice thickness). Elliptical k-space sampling, partial Fourier encoding, over-contiguous slice spacing and partial echo acquisition were used to improve temporal resolution (4.97 s for the DCE-MRI series). Total imaging time for DCE-MRI was 7 min 33 s. Tumour T1 was calculated using the variable flip angle method. An arterial input function was measured where possible; alternatively a population-derived function was used. The following parameters were then calculated for each voxel: (1) tumour volume (2) T1 (3) enhancing fraction (E_fraction) (the ratio of enhancing voxels to total number of tumour voxels), (4) the volume transfer constant (K_trans), (5) blood plasma volume (v_p) and (6) volume of the extracellular extravascular space (v_e).

Relative change from mean baseline values was expressed as a percentage change for each parameter at four and 48 hours and days 8 and 12. A mixed effects model was used to examine the interaction of changes across the cohort, since some patients had multiple tumours. Due to the large number of parameters analyzed, p values less than 0.01 were considered statistically significant. All p values were two-tailed and were not formally adjusted for multiple comparisons. Repeatability was examined by measuring percentage within subject coefficient of variation and percentage smallest detectable change (SDC) in a single tumour.

**Results and Discussion**

Reductions in E_fraction and K_trans were detected throughout the cycle of bevacizumab (Figure 1). In particular, statistically significant reductions in tumour E_fraction were measured at 48 hours (p=0.004) and maintained at day 8 (p=0.0005) and day 12 (p=0.0026). These changes were accompanied by reductions in K_trans at the corresponding time points. No significant changes were detected in any parameter in skeletal muscle at any time points, indicating that it is unlikely that a systemic homodynamic response – affecting all tissues – accounted for the response measured within the tumours. These changes concur with previous studies which demonstrated reductions in tumour blood flow and blood volume 12 days after infusion of bevacizumab in five patients with rectal cancer. Here, we demonstrate that these changes occur rapidly, are statistically significant within 48 hours and persist throughout the entire cycle of therapy.

Our data demonstrates statistically significant decrease in median K_trans at 4 hours (p=0.0012) and that K_trans remained reduced at 48 hours and at day 8. These reductions were not sustained at day 12 (Figure 1). The decoupling of K_trans changes from E_fraction changes at day 12 suggests that K_trans is more sensitive to functional changes in the tumour vasculature rather than structural changes.

**Conclusions**

Our data demonstrates statistically significant early reductions in the parameters E_fraction and K_trans that remain throughout a single cycle of anti-VEGF monotherapy. These changes are considered to reflect structural changes in tumour vasculature. In distinction, measures of the measured reductions in K_trans were transient and representative functional changes. Measured anti-vascular effects led to subsequent resolution of oedema and tumour shrinkage. These data (1) highlight the importance of performing multi-parameter analysis on DCE-MRI data beyond that restricted to K_trans and/or IAUGC alone; and (2) demonstrate the need to optimise measurement timing when applying quantitative imaging to trials of novel therapeutic agents.

**Acknowledgements**