Evaluating the Early Effects of Anti-angiogenic Treatment in human breast cancer with Intrinsic susceptibility-weighted and Diffusion-weighted MRI: initial observations

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Introduction

Bevacizumab (Avastin, Roche, UK) is an anti-VEGF antibody that targets abnormal tumour neovasculature reducing vascular permeability and extracellular leakage space [1]. Both Diffusion-weighted (DW) and Intrinsic susceptibility-weighted (ISW) MRI methods have the potential to detect early treatment effects related to vascular shutdown and cellularity, and hypoxia respectively. Increases in ADC values (apparent diffusion coefficient) resulting from cell death have previously been observed with chemotherapy in primary breast cancer [2]. Increases in R_2* have also been demonstrated in response to neoadjuvant chemotherapy in breast cancer [3]. In this study, we evaluate changes in R_2*, ADC and DCE-MRI derived kinetic parameters after one dose of neoadjuvant bevacizumab in chemotherapy naïve human breast carcinomas.

Methods

17 patients with primary breast carcinoma (median age 47 years; range 35-59; T2-4, N0-1, M0) were treated with one single dose of bevacizumab (15mg/kg, intravenously) prior to receiving neoadjuvant chemotherapy as part of a two-centre, phase II, non-randomised clinical trial. Spoiled multi-echo T_2*-weighted sequences (TE 5-75 ms, TR 100 ms, flip angle (α) 40˚, 8mm slice thickness, FOV 260mm, 256^2 matrix) were acquired after lesion localisation using conventional non-contrast enhanced sequences. DW-MRI was performed using b-values of 0 and 800 s.mm^2 in 12 directions. T_1-weighted DCE-MRI sequences (TE 4.7 ms, TR 11 ms, α 35˚, 256^2 matrix) were also performed using 0.1mmol/kg body weight of Gd-DTPA. R_2* values were calculated using a least-squares fitting routine on *ln*[signal] plotted against TE. DCE-MRI images were analysed with specialist MRIW software (Institute of Cancer Research, London) [4] using Tofts' pharmacokinetic model [5] and a population arterial input function (modified Fritz-Hansen) [6]. Whole tumour ROI parametric values were acquired for R_2* (s^{-1}), ADC (μm^2.s), and DCE-MRI parameters $IAUGC_{60}$ (mmol.s), transfer constant (K^{trans}; min^{-1}), leakage space (v_e; %) and rate constant (k_{ep}, min^{-1}). Relationships between MRI parameters at baseline were explored with Spearman's rank correlation. Changes in parameters after treatment with Bevacizumab were assessed for significance using paired Student's t-testing. Significance was assigned at a p value of ≤ 0.05

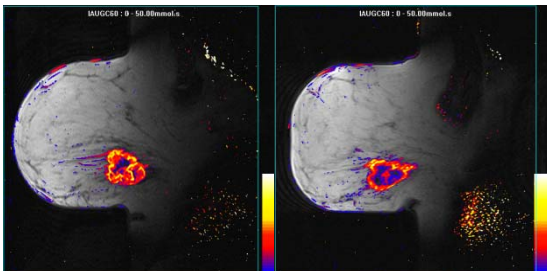

Fig 1: Parametric maps of $IAUGC_{60}$ pre and post-bevacizumab

Parameter	Baseline	Post-bevacizumab	t-test
ADC (μm^{-2})	1050 (882-1482)	1028 (739-1210)	p=0.028
$IAUGC_{60}$ (mmol.s)	20.17 (9.64-29.14)	14.26 (7.40-17.95)	p<0.001
K^{trans} (min^{-1})	0.33 (0.15-0.68)	0.23 (0.05-0.26)	p=0.001
v_e (%)	43.6 (32.7-68.7)	43.3 (12.9-68.5)	p=0.355
k_{ep} (min^{-1})	0.70 (0.37-1.72)	0.48 (0.26-0.81)	p=0.003
R_2* (s^{-1})	30.7 (17.9-38.6)	32.4 (19.9-48.5)	p=0.003

Table 1: Baseline and post-bevacizumab values for ADC, DCE-MRI kinetic parameters, R_2*

Results

17 patients were imaged at baseline and two weeks after bevacizumab. A positive correlation between ADC and v_e was observed at baseline (ρ = 0.50, p = 0.049). After treatment with bevacizumab, there were significant reductions in $IAUGC_{60}$, K^{trans} and k_{ep} (n=16) (table 1), except for one patient in whom, an increase was noted (Fig 2). Of the 15 patients available for DW-MRI analysis, significant reductions in values for ADC were seen in 13 (Fig 2). In contrast, increases were observed in two patients whose tumours exhibited macroscopic central necrosis on ADC maps, morphological images and on DCE-MRI scans. There were increases in R_2* values after treatment (p=0.007) (n=15); two patients were excluded for the purposes of analysis due to confounding changes in R_2* caused by macroscopic necrosis [3].

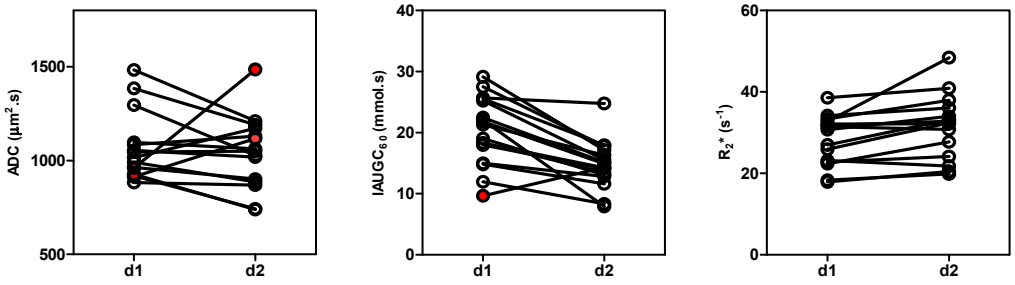

Fig 2: Ladder plots for changes in (a) ADC, (b) $IAUGC_{60}$ and (c) R_2* from baseline (d1) to post-treatment (14 days after bevacizumab) (d2). Red dots indicate in (a) 2 patients in whom their tumours became necrotic and in (b) 1 outlier

Discussion

Reductions observed in ADC and $IAUGC_{60}$, K^{trans} and k_{ep}, accompanied by increases in R_2* are consistent with anti-vascular effects achieved with bevacizumab alone. Decreases in ADC are most likely explained by reductions in tumour perfusion with reductions in the extracellular space possibly also contributing to these changes (although v_e changes in this study were not significant). In contrast, tumours which become necrotic in response to anti-angiogenic therapy exhibited increases in ADC. Accordingly, increases in R_2* are also seen as a result of reductions in tumour perfusion leading to tumour hypoxia. DCE, DW and ISW-MRI changes after one dose of bevacizumab can serve as early biomarkers of anti-angiogenic action in primary breast cancers.

References: [1] Wedam SB, et al. J Clin Oncol.2006;24(5):769-77 [2] Park SH, et al. Radiology 2010;257:56-63 [3] Li SP, et al. Radiology 2010:epub ahead of print [4] d,'Arcy JA, et al. Radiographics 2006;26(2):621-32 [5] Tofts PS. JMRI 1997; 7(1):91-101[6] Walker-Samuel S, et al. Phys Med Biol 2007;52:589-601