DCE-MRI demonstration of antivascular effects of combretastatin A4 phosphate (CA4P) given in combination with bevacizumab to human subjects with advanced solid tumours

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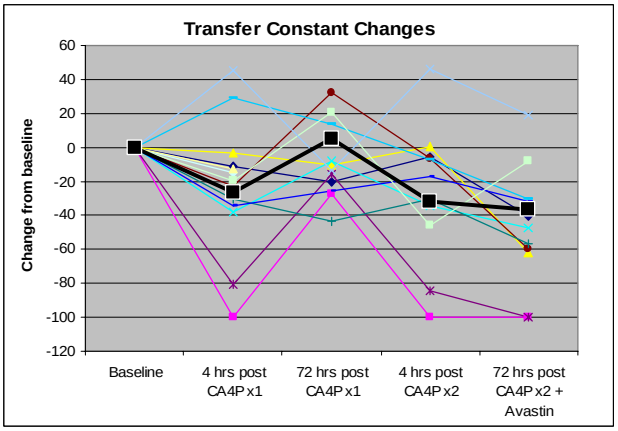
Aims: To measure variability of T_1-weighted DCE-MRI in a multicentre study, to document reversible tumour vascular shutdown following the first administration of the vascular disruptive agent (CA4P), and to show failure of recovery of tumour vasculature when CA4P is given with the anti-VEGF antibody bevacizumab.

Introduction: The vascular disruptive agent (VDA) CA4P induces significant tumour necrosis as a single agent. Vascular shutdown is reversible and tumours re-grow due to persistent vascularisation of the surviving tumour rim. Pre-clinical models have demonstrated that the addition of an anti-VEGF antibody to a VDA significantly increases anti-tumour activity, possibly by inhibiting neo-vascularization of the surviving rim [1]. The purpose of this first clinical study combining a VDA with an anti-angiogenic drug was to establish the safety of the CA4P / bevacizumab combination and to demonstrate synergy of action *in-vivo* using DCE-MRI.

Patients and Methods: A phase 1 dose escalation study was performed in 2 UK centres. Patients with advanced solid malignancies in 3 cohorts were recruited to receive CA4P (45mg/m^2, 54mg/m^2, 63mg/m^2). 3 patients per cohort were recruited unless dose-limiting toxicity (DLT) was seen in which case the cohort was expanded to 6. In the 1st cycle of treatment, only CA4P was administered. Bevacizumab (10mg/kg) was given 4 hours after CA4P in a subsequent 2 weekly cycle. DCE-MRI was performed at baseline (x2), after CA4P alone (4 and 72 hrs), after the 2nd dose of CA4P (4hrs) and after the 1st dose of bevacizumab (72 hrs) in the 1st cycle. Circulating endothelial cells (CECs) and progenitors (CEPs) were enumerated and serum/plasma cytokine biomarkers were measured.

DCE-MRI: Patients were imaged on 1.5T Siemens Symphony/Avanto scanners. Anatomical images were used to identify tumour slice locations, T_1W spoiled 3D GRE [FLASH] sequences were acquired before and after the bolus administration of 0.1 mmol/kg b.w. of Gd-DTPA every 12 seconds measured sequentially over 8 min. Images were registered to proton-density weighted images to enable the calculation of changing tissue T_1-relaxivities and contrast agent concentrations [2]. System measurement gain and scaling factors were maintained between acquisitions of PD and T_1W dynamic series of images. ROIs were placed around the whole tumours to calculate pixel-by-pixel values of transfer constant (K^{trans}) using the methods of Tofts [3] on MRIW software [4] using a pooled AIF (Modified Fritz-Hansen [5]). Initial area under Gd-DTPA curve at 60 seconds ($IAUGC_{60}$) was also calculated. Lesion inclusion criteria were: lesion >2 cm in size, single organ, no partial volume averaging but no more than 5 lesions/organ.

Results: 10 of 12 scheduled patients have been recruited to date. 1 patient dataset was excluded because of marked motion artefacts. 13 lesions in 9 patients were used in this analysis. Excellent reproducibility was obtained (within patient coefficient of variance and coefficient of reproducibility (n=1) for K^{trans} and $IAUGC_{60}$ = 5.0%/18.1% and 8.9%/24.7% respectively). Seven, 5 and 9 of 13 lesions showed significant reductions in K^{trans} following CA4P 1st dose, CA4P 2nd dose and after bevacizumab respectively (figure). Group changes (black line in figure) were significantly reduced at these time points. Initial analysis of the first cycle shows highly significant elevations of vascular endothelial growth factor (VEGF) and stromal derived growth factor (SDF1) 4 hours after CA4P, returning to baseline by 24 hours.



Conclusions: This is the first mechanistic demonstration in humans of increased anti-vascular action of CA4P and bevacizumab. Although there is marked heterogeneity in individual lesion DCE-MRI responses, cohort analysis convincingly shows failure of tumour vasculature to recover when CA4P is given with bevacizumab. Final data regarding circulating endothelial cells/circulating endothelial progenitors/cytokines and pharmacokinetics is awaited.

References:

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