An exploratory open-label, non-randomised, single centre methodology study to compare dynamic contrast enhanced CT and MRI as markers of changes in vascular activity mediated by a positive control agent (Cediranib), a potent inhibitor of VEGF-driven angiogenesis in patients with advanced solid tumours

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Introduction: Dynamic contrast enhanced (DCE) imaging with MRI or CT allows functional assessment of tumour vascularity and is used to evaluate response to anti-vascular and anti-angiogenic targeted agents. While DCE-MRI has the advantages of multi-planar data acquisition, lack of ionising radiation and high tissue contrast, DCE-CT has the benefit of speed, and thus increased patient compliance with more robust quantitation. The aim of this study therefore was to establish the within patient variability of DCE-MRI vs. DCE-CT in the same patients and compare their ability to measure changes in tumour blood flow and permeability in these patients when treated with the VEGFR tyrosine kinase inhibitor cediranib.

Methods: ***Patients***: 29 patients with metastatic tumours refractory to standard therapies and at least one lesion size ≥ 3cm suitable for repeat assessment by DCE-MRI and DCE-CT were studied. 28 patients were evaluable for reproducibility, 27 patients were evaluable for changes at day 7 of which 14 patients received cediranib 45mg/day and 13 patients received cediranib 30mg/day. ***Imaging Timing***: Baseline DCE-MRI and DCE-CT was performed at two time points not more than 7 days apart prior to first dose of drug. Follow-up DCE-MRI and DCE-CT was performed at the same time-point within 7 days of the first dose. ***Imaging protocols***: DCE-MRI: Data were acquired at 1.5T (Siemens Avanto) using Magnevist 0.2mg/kg injected at 3mls/sec followed by 20mls saline at 3mls/sec as a contrast agent. For abdominal sites data were acquired coronally in sequential breath-hold at expiration using a 3D FFE sequence, which gives highly reproducible registration of the liver (Orton et al). Imaging parameters were TR/TE = 3.05/0.89 ms, FA = 16^0, 14×5mm slices NSA = 1, IPAT = 2, FOV = 308x320mm, 208x256 matrix. Two image volumes were acquired during each 6 sec breath-hold, followed by a 6 sec breathing gap, and 40 volumes were acquired over a 4 minute period. The dynamic scan was preceded by a calibration scan with the same parameters except FA = 3^0 to enable the dynamic sequence to be converted to contrast agent concentration. In the pelvis a free-breathing technique with same imaging parameters acquired 80 image volumes continuously at 3.3 sec/vol for 4.3 min. DCE-CT: Data were acquired on a GE Lightspeed (GE Healthcare Technologies, Waukesha, WI) with iv Omnipaque 300 0.5ml/kg at 3-5mls/sec followed by 20 mls saline at 3-5mls/sec; 20x5mm slices over lesion of interest were obtained pre-contrast. After a 5 second delay, a breath hold cine covering 4x5mm at 0.5 sec/volume in the centre of a lesion of interest over 55 sec with 120KV 60MA was obtained; following this twelve breath hold 4x5mm slices at 120KV and 60MA were acquired at 10 second intervals. ***Data Analysis***: MRI: Data were analysed using MRIW (in house software using extended Tofts model). Regions of interest (ROIs) were drawn by a radiologist and the following parameters derived: Initial Area Under the Curve for the first 60 seconds (iAUC60 mMol.sec), volume transfer constant between plasma and extracellular space (Ktrans min^{-1}), volume of extracellular-extravascular space (EES) per unit volume of tissue (Ve ml/ml), flux rate constant between EES and plasma (Kep min^{-1}), blood plasma volume per unit volume of tissue (Vp ml/100g), and Enhancing Fraction (EF, ml/ml), defined as the proportion of voxels where every point of the uptake curve between 30 and 90 seconds post-onset is more than 1 sd above the mean pre-enhancement value. CT: Data were analysed using GE Perfusion 3 Software (based on St Lawrence and Lee model). ROIs were drawn by a radiologist and the following parameters derived: Permeability Surface Product (PSP ml/min/100g), Perfusion (F ml/min/100g), Mean transit Time (MTT sec), Blood Volume (Vp ml/100g), Positive Enhancement Integral (PEI Hus). ***Statistics***: Baseline was defined as the geometric mean of two measurements obtained prior to the start of daily dosing with cediranib. If data were only available at one time-point prior to the start of daily dosing with cediranib, this was used as the baseline value. The variability between the baseline DCE-MRI and DCE-CT values for each patient was estimated with inter- and intra-subject components of variation using an analysis of variance (ANOVA) model. Effects of cediranib were assessed by measuring the change from baseline in parameters obtained from DCE-MRI and DCE-CT. An ANOVA model was fitted to the natural logarithm-transformed change from baseline DCE-MRI or DCE-CT parameter measurement, with treatment (starting dose) included as a term in the model.

Results:

Method	Parameter	Baseline Value Analysis (n=29)			Change from baseline at day 7 (n=27)			
					Cediranib 45mg		Cediranib 30mg	
		Mean difference	95% CI	Within pt CV	Mean % change	95% CI	Mean % change	95% CI
DCE-MRI	EF (Volume)	-4.6	-9.0, -0.1	8.6	-43.8	-57.3,-26.0	-22.3	-41.2, 2.7
DCE-MRI	Ktrans(median)	-5.6	-12.5,1.8	13.9	-61.6	-73.3,-44.4	-51.0	-66.2,-29.1
DCE-MRI	iAUC60(median)	-3.1	-10.9,5.4	15.5	-66.0	-79.6,-43.5	-44.9	-67.3,-7.3
DCE-MRI	Kep(median)	-0.9	-11.8,11.3	21.4	-36.6	-51.2,-17.6	-31.9	-48,-10.9
DCE-MRI	Ve(median)	-3.1	-14.5,9.7	23.1	-23.8	-42.1,0.4	-7.7	-30.6,22.8
DCE-MRI	Vp(median)	-32.3	-69.2,48.7	262.0	-57.1	-82.2,3.5	-36.3	-74.2,57.1
DCE-CT	PEI(median)	-1.9	-10.1,7.1	16.0	-26.2	-39.1,-10.5	-28.7	-41.6,-12.9
DCE-CT	MTT(median)	1.1	-7.7,10.8	16.8	-1.0	-12.6,12.3	6.8	-6.3,21.6
DCE-CT	Vp(median)	-0.2	-11.8,12.8	22.7	-49.4	-61.7,-33.1	-47.2	-60.5,-29.4
DCE-CT	F(median)	-1.8	-13.5,11.4	23.3	-39.4	-57.1,-14.2	-43.8	-60.8,-19.5
DCE-CT	PSP(median)	0.5	-14.3,17.9	29.6	-54.3	-66.6,-38.1	-53.9	-66.4,-36.8

(CI: Confidence Interval; CV: Coefficient of variation).

Discussion: Image parameters were reproducible (<30% within patient CV), most were in the range 15-25%, except for Vp measured by DCE-MRI. The most reproducible parameter was DCE-MRI EF followed by DCE-MRI Ktrans and iAUC60, and DCE-CT PEI. The only statistically significant average change between measurements obtained prior to first dose of drug was for the EF parameter. Both DCE-MRI and DCE-CT generate highly reproducible measurements of vascular physiology. On average, cediranib reduced tumour blood flow, permeability and EF at day 7 with changes in DCE-MRI (iAUC60 and Ktrans) consistent with those reported in other studies with cediranib (Drevs et al). DCE-MRI and DCE-CT were comparable when assessing changes from baseline in vascular physiology. There was generally a higher percentage change from baseline for MRI for parameters measuring area under the curve (iAUC60, PEI). On average percentage change from baseline for parameters reflecting permeability and blood flow were comparable (Ktrans vs PSP and Ktrans vs F). Percentage reductions from baseline for blood volume were generally larger and more consistent for CT than MRI. **References:** Orton MR et. al. Phys Med Biol. 2009;54:2197-2215. Drevs J et al. JCO 2007;25:3045-54.

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