Diffusion weighted imaging detects significant cohort responses after seven days of treatment with Cediranib in a phase I clinical trial setting

Matthew R Orton[1], Christina Messiou[2], David J Collins[1], Veronica Morgan[2], Dionysis Papadatospastos[3], Andre Brunetto[3], Jooern Ang[3], Helen Mann[4], Jean Tessier[4], Helen Young[4], Stan Kaye[3], Johann de Bono[3], Martin O Leach[1], and Nandita de Souza[1]

[1]CR-UK and EPSRC Cancer Imaging Centre, Institute of Cancer Research, Sutton, Surrey, United Kingdom, [2]Radiology Department, Royal Marsden NHS Foundation Trust, Sutton, Surrey, United Kingdom, [3]Department of Medicine, Royal Marsden NHS Foundation Trust, Sutton, Surrey, United Kingdom, [4]AstraZeneca, Macclesfield, Cheshire, United Kingdom

Introduction The role of DCE-MRI derived measures for assessing the perfusion status of tumours in response to vascular targeted agents is established. In a recently reported study of Cediranib (a potent inhibitor of the tyrosine kinase activity of multiple VEGF receptors [1]) comparing the performance of DCE-MRI against DC-CT for assessing vascular activity in a phase I trial setting, we demonstrated changes after 7 days of treatment [2]. Diffusion weighted images (DWI) obtained as part of this study offer the opportunity to evaluate the response of DWI derived measures after 7 and 28 days of treatment with this antiangiogenic agent. Although DWI measures have previously been reported demonstrating changes with anti-angiogenic agents at 28 days, the response at 7 days has not been widely reported as it has been assumed that DWI is not sensitive to the perfusion changes seen with an antiangiogenic agent in such a short time-frame. The purpose of this study was to document changes in DWI derived measures at both 7 and 28 days for a cohort of patients treated with Cediranib.

Data Acquisition and Processing *Subjects and Timing:* 29 patients with metastatic disease refractory to standard therapies and at least one lesion ≥3cm suitable for repeat assessment by DCE-MRI and DC-CT were enrolled. Patients received daily Cediranib treatment with 14 patients starting treatment at 45mg and 15 at 30mg. Two baseline measurements were performed 7 days apart, within 14 days of starting treatment. Follow-up measurements were performed within 7 days and within 28 days of the first dose. For more details see [2]. *Imaging*: Diffusion weighted images were acquired in free-breathing with a 1.5T Siemens Avanto MR system using an axial multi-slice EPI sequence. Parameters were: TR/TE = 3500/69 ms, 20×5mm slices, NSA = 6, GRAPPA factor = 2, 380×380 mm FOV, 128×128 matrix, 6/8 PE partial acquisition, SPAIR fat suppression, 3-scan trace images, six b-values (0, 50, 100, 250, 500, 750 s/mm^2), total acquisition time 6 min 51 sec. *Data Analysis*: 27/29 patients had evaluable DWI data and were included in this study. One exclusion was because the patient had a stent and so DWI images were not acquired, the other was due to failure of the DWI acquisitions. Regions of interest were drawn on the b = 500 s/mm^2 image on all slices in which the tumour appeared, which gave full tumour coverage in 19/27 patients – the remainder had large tumours extending outside the 100mm coverage. The parameters in the table below were derived by least-squares fitting a mono-exponential, stretched-exponential [3] and double-exponential (IVIM) [4] model to the attenuation curve in each voxel, and the median value was reported for each volume. Repeatability of the various measures was assessed using the coefficient of variation (CV). Equivalent 95% confidence interval for changes in a cohort of 27 patients (Cohort 95% CI) were also derived and these define ranges of statistically insignificant changes from baseline. Percentage changes to the mean cohort measures were calculated at days 7 and 28 and those falling outside the 95% CI were considered to be significant (figures in brackets give the 95% CI of the cohort change, reflecting between-patient variation). Significant changes are highlighted in dark grey, those of borderline significance are in lighter grey. (Note : No adjustment has been made for testing multiple endpoints at two time points, leading to an increase in the chance of a false positive, caution is required in interpretation of results.)

Results and Discussion The table shows that early and late treatment changes in both ADC measures and in DDC (distributed diffusion coefficient for the stretched exponential model) are consistent with the hypothesis that an antiangiogenic intervention will not give significant changes until day 28, although the change at day 7 for ADC (b≥0) is of borderline significance. However, changes in α are clearly significant and have a similar increase at both time-points. In this study, cohort reductions were seen in K^{trans} – a DCE-MRI

Model	Parameter	CV(%) (N=27)	Cohort 95% CI (%) (N=27)		Cohort change (%) day 7 (N = 26)		day 28 (N = 24)	
Mono Exponential	ADC (b≥0)	4.2	-1.57	1.60	-1.69	(-4.5, 1.2)	6.76	(0.95, 13)
	ADC (b≥100)	3.91	-1.46	1.49	0.807	(-2.1, 3.8)	9.8	(4.4, 16)
Stretched Exponential	DDC	4.75	-1.78	1.81	-0.598	(-3.7, 2.6)	8.8	(2.0, 16)
	α	4.14	-1.55	1.57	5.85	(3.5, 8.3)	6.36	(3.2, 9.6)
Double Exponential (IVIM)	D	6.04	-2.25	2.30	-1.33	(-6.0, 3.6)	9.7	(2.1, 18)
	f	22.4	-8.02	8.71	-9.05	(-20, 3.9)	-19.8	(-33, -4.3)
	D*	44.4	-14.80	17.30	-30.6	(-41, -18)	-15.5	(-47, 34)
	f·D*	6.42	-2.39	2.45	-8.77	(-13, -4.1)	-0.0587	(-3.4, 3.4)

measure sensitive to perfusion and vascular permeability – that were also of a similar magnitude at both time-points (day 7 = -56.1%, day 28 = -49.7%, combined 30 and 45mg dose groups [2]). The IVIM model for diffusion attenuation suggests that DWI data at low b-values are sensitive to perfusion effects, and so it is plausible that changes in α are influenced by tumour perfusion. To explore this hypothesis a double exponential (IVIM) model was fitted to the data. Double exponential estimates indicated that *f* decreased at both time-points, but that the sizes of change at the two time-points were quite different. *D** and *f·D** also had significant decreases at day 7, but not at day 28. These treatment effect patterns did not resemble those of K^{trans}, indicating that the biological mechanism for the statistically significant changes seen at day 7 may be unrelated to mechanisms affecting K^{trans}. Unfortunately the b-values used in this study were not optimal for an IVIM measurement, as evidenced by the large CV for *D**.

Conclusions Statistically significant cohort changes are detected by DWI measurements after just 7 days of treatment with an antiangiogenic agent in a typical phase I patient population. Significant changes in measures reflecting simple diffusion are seen at day 28 but not day 7, consistent with their link to tumour cellularity. The stretched exponential is recommended for use in this setting as both parameters of the model have good repeatability, the DDC parameter has a similar response to the pure diffusion measures (ADC and *D*), and the stretching parameter α is sensitive to the changes in the DWI measurements at both time-points.

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