Serial R_2* MRI to Evaluate Response to Tumour Vascular Disruptive Treatment in a Clinical Phase I Trial

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Introduction

OXi4503 (combretastatin A1 phosphate, CA1P: OXiGENE, Inc., San Francisco, CA, USA) is a tubulin-binding vascular disruptive agent (VDA) that destroys pre-existing blood vessels of tumours, leading to rapid shutdown of the tumour's blood supply. Dynamic contrast enhanced MRI (DCE-MRI) studies of other VDAs have generally evaluated pharmacodynamic effects after 3-4 hrs of drug administration; this time point is arbitrarily chosen. However, animal data indicate a rapid onset of action of VDAs [1] but the optimal time for imaging vascular shutdown in human tumours is unknown. Robinson et al. have shown that the intrinsic susceptibility MRI parameter R_2* can be used to non-invasively detect VDA activity in animal models when measurements are repeatedly acquired [2,3]. In this still ongoing, translational phase I clinical trial of OXi4503, we have replicated Robinson's methods by undertaking repeated R_2* measurements during the 1st 4 hours after OXI4503 administration. Changes observed in R_2* were used to define onset of VDA activity and results are compared to DCE-MRI changes at 4 hours.

Patients and Methods

Patients with advanced tumours refractory to standard therapy were treated with escalating doses of OXi4503 from 0.06 to 11 mg/m^2 body surface area as a weekly infusion on 3 of 4 weeks per cycle. MRI was performed using a 1.5T Siemens Symphony scanner. A spoiled multi-echo T2*-weighted MRI sequence (TE 5-75ms, TR100ms, flip angle (α) 40˚, 8mm slice thickness, FOV 260mm, 256^2 matrix) was used. T1-weighted DCE-MRI sequences (TE 4.7ms, TR 11ms, α 35˚, 256^2 matrix) were also performed using 0.1mmol/kg bw of GD-DTPA. DCE-MRI images were analysed with specialist MRIW software (Institute of Cancer Research, London) using Tofts' pharmacokinetic model [4] and a population arterial input function (Modified Fritz-Hansen [5]. Whole tumour DCE-MRI kinetic parameters (K^{trans}, $IAUGC_{60}$), and R_2* were calculated.

Two MRI scans (DCE-MRI and R_2*) were performed within 8 days prior to treatment to establishes reproducibility. R_2* measurements were obtained every 45-60 mins for up to 4 hours. DCE-MRI was performed after 4 hours. Patients were grouped by DCE response at the 4 hr time-point (DCE responder/non-responder) and by drug dose (high dose/low dose). Group and individual lesion changes were assessed for significance from the calculated reproducibility using methods of Galbraith [6].

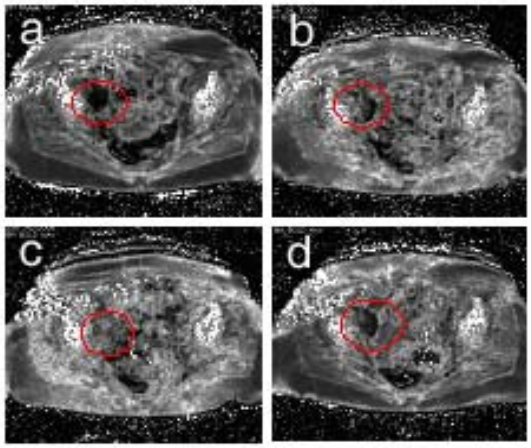

Figure 1: Ovarian cancer (red circle) metastasis in right side pelvic lymph nodes R_2* images at a) baseline, b) 1½ hrs, c) 3 hrs, and d) 4 hrs after OXi4503 infusion (8.5 mg/m^2). After an initial increase in R_2* there is a decrease noted by 4hrs.

Results

16 patients with 21 lesions were evaluable. R_2* images of one patient is shown in Figure 1. Threshold values (n=1) were: R_2* ±16.9%; K^{trans} -16.04%; $IAUC_{60}$ ±17%. When patients are grouped by drug dose (high dose (8.5-11 mg/m2; n=9) vs. low dose (0.06-6.5 mg/m2; n=12) significant increases in group R_2* are seen between 2-4 hours (Figure 2) in the high dose group. Interestingly, significant differences in DCE-MRI parameters are also noted consistent with a drug dose-DCE-MRI response relationship. However when patients are grouped by DCE-MRI response (judged by significant decreases in K^{trans} and/or $IAUGC_{60}$ at >4hrs) there were less consistent group R_2* changes although individual responding patients were seen in both groups. If both R_2* and DCE-MRI parameters are used to assess OXI4503 activity (by significant increases in R_2* and decreases in K^{trans}/$IAUGC_{60}$), then 11 of 21 (52%) lesions show MRI changes consistent with VDA effect.

Discussion and Conclusion

This is the first, in-human study of serial BOLD MRI after a VDA, indicating that R_2* shows significant VDA action within the 1st few hours after OXI4503. Both R_2* and DCE-MRI show positive dose-response relationships. We were surprised to find a disconnection between temporal changes in R_2* and static time point DCE-MRI change. This may be explained in part by the transient nature of the R_2* change in DCE-MRI non-responders. In DCE-MRI responders, vascular collapse can empty blood vessels of red blood cells and therefore paradoxically lower R_2*.

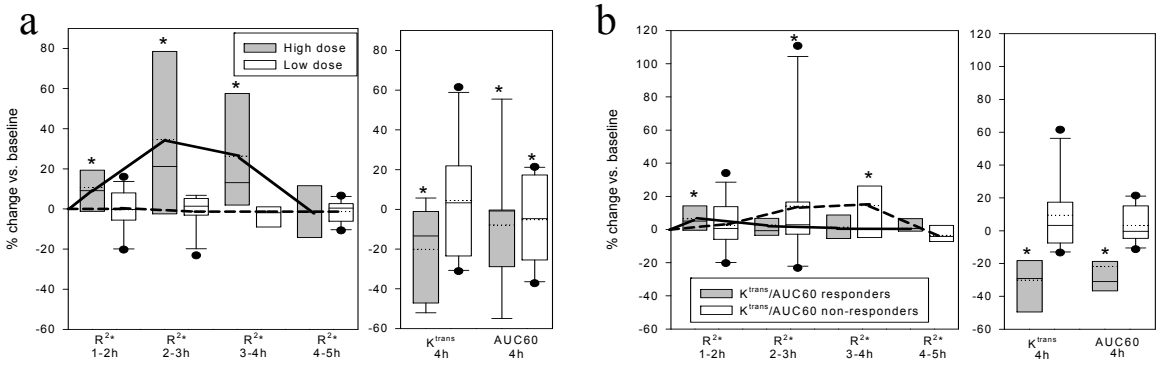

Figure 2: Box plots for changes in R_2* at different time points with patients grouped by drug dose (a) and DCE response (b). (a) When patients are grouped by drug dose (high dose (n=9) vs. low dose (n=12) significant increases in group R_2* are seen between 2-4 hours. Interestingly, significant differences in DCE-MRI parameters are also noted. (b) When patients are grouped by DCE-MRI response there are less marked differences in R_2* between the two groups. *p<0.05.

[1] Maxwell RJ et al, *NMR Biomed.* 2002 Apr;15(2):89-98 [2] Robinson SP et al, *Neoplasia*. 2005 May;7(5):466-74 [3] McPhail LD et al, *Int J Radiat Oncol Biol Phys*. 2007 Nov 15;69(4):1238-45. [4] Tofts PS. *JMRI* (1997)**7**(1): 91-101. [5] Walker-Samuel S. et al. *Phys Med Biol* 2007, **52**:589-601. [6] Galbraith SM et al, *NMR Biomed.* 2002;**15**:132–142