Serial R_2* MRI to Evaluate Response to Tumour Vascular Disruptive Treatment: Final Results of a Clinical Phase I Trial

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Introduction

The tubulin-binding vascular disrupting agent (VDA) OXi4503 (combretastatin A1 phosphate, CA1P) destroys pre-existing blood vessels of tumours, leading to rapid shutdown of the tumour's blood supply. For the evaluation of pharmacodynamic effects of other VDAs, dynamic contrast enhanced MRI (DCE-MRI) studies have been performed after 3-4h of drug administration. 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 [1,2]. In the now completed translational phase I clinical trial of OXi4503, we performed repeated R_2* measurements during the first 4 hours after the first OXi4503 administration.

Patients and Methods

Patients with advanced tumours refractory to standard therapy were treated with escalating doses of OXi4503 from 0.06 to 14 mg/m^2 body surface area as a weekly infusion on 3 of 4 weeks per cycle. MRI was performed using a 1.5 T 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 [3] and a population arterial input function (Modified Fritz-Hansen [4]). 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 establish reproducibility. R_2* measurements were obtained every 45-60 min for up to 4 hours; intermittent repositionings of the patients were undertaken and R_2* images were replanned on new morphological sequences. DCE-MRI was performed after 4 hours. Patients were grouped by drug dose (low dose [0.06-5 mg//m^2]/intermediate dose [6.5-11 mg//m^2]/high dose [12.5-14 mg//m^2]) and by DCE response at 4h (no K^{trans}-decrease, non-significant K^{trans}-decrease, or significant K^{trans}-decrease). Group and individual lesion changes were assessed for significance from the calculated reproducibility using methods of Galbraith [5].

Results

22 patients with 27 lesions were evaluable. K^{trans} and R_2* images of three patients are shown in Figure 1. Threshold values (n=1) were: K^{trans} -14%; R_2* ±43.31%. When patients are grouped by drug dose (low dose [n=8], intermediate dose [n=8], and high dose [n=11]), significant increases in group R_2* are seen at 24 hours and 8 weeks in the intermediate and high dose group only. Interestingly, significant increases in R_2* at 3h and 4h were only seen in the intermediate dose group (Figures 1B and 2A). When patients are grouped according to K^{trans} response (no K^{trans} decrease; n=8, non-significant K^{trans} decrease; n=8, significant K^{trans} decrease; n=11), early R_2* changes were only seen in patients with non-significant K^{trans} decreases (Figure 2B).

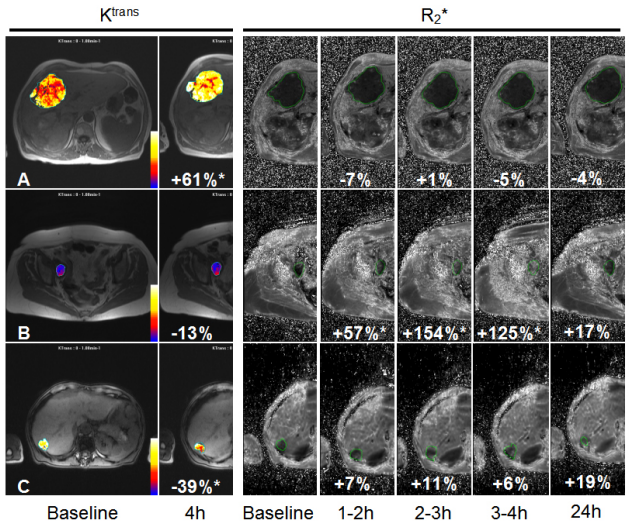

Figure 1: K^{trans} maps at baseline and at 4h, and R_2* maps at baseline and at 1-2h, 2-3h, 3-4h, and 24h after OXi4503 infusion in a patient with liver metastasis of pancreatic cancer treated at low dose (3.84 mg/m^2) (A), in a patient with pelvic metastasis of melanoma at intermediate dose (8.5 mg/m^2) (B), and in a patient with liver metastasis of epithelial ovarian cancer at high dose (14 mg/m^2) (C).
Only in the patient with a non-significant K^{trans}-decrease treated at intermediate dose (B), but neither in the patient with no K^{trans}-decrease, treated at low dose (A), nor in the patient with significant K^{trans}-decrease, treated at high dose, a significant increase in R_2* is seen.
Numbers indicate the %-change in K^{trans}, and R_2*, respectively.

Discussion and Conclusion

This is the first, in man study of serial BOLD-MRI after a VDA, indicating that R_2* shows significant VDA effect within the first few hours after OXi4503. DCE-MRI showed a significant dose - response relationship (data not shown). The findings with R_2* were surprising in that it was only the group with non-significant K^{trans}-decreases, treated at intermediate doses, that showed significant increases in R_2*. The mechanistic explanation may be that at intermediate doses, deoxygenated erythrocytes become entrapped within the tumour vasculature. At higher doses there is marked vascular collapse resulting in the emptying of blood vessels of red blood cells and therefore paradoxically not changing the R_2*. Both K^{trans} and R_2* are recommended as MR biomarkers for evaluating VDAs.

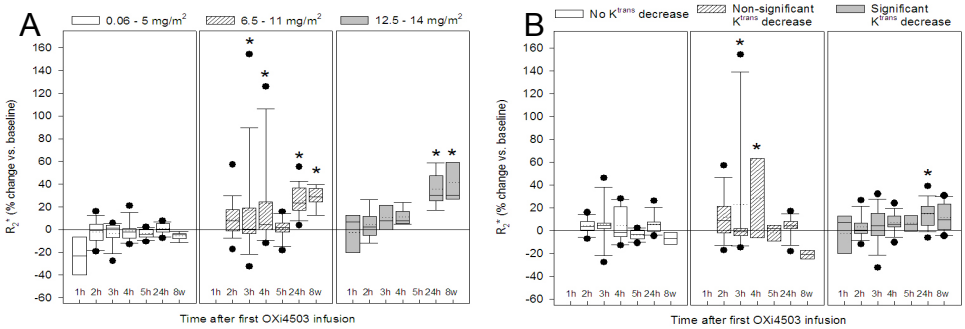

Figure 2: Box plots for changes in R_2* at different time points with patients grouped by drug dose (A) and DCE response at 4 hours (B). When patients are grouped by drug dose (low dose [n=8], intermediate dose [n=8], and high dose [n=11], significant increases in group R_2* are seen at 24 hours and 8 weeks in the intermediate and high dose group only (*). Interestingly, significant increases in R_2* at 3h and 4h is only seen in the intermediate dose group (A). Early R_2* changes were only seen in patients with non-significant K^{trans} decreases (B). *p<0.05.

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

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