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/m² 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, TR:100ms, flip angle (α) 40°, 8mm slice thickness, FOV: 260mm, 256* matrix) was used. T1-weighted DCE-MRI sequences (TE:4.7ms, TR:11ms, α:35°, 256* 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 ($K_{trans}$, IAUGC0), 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/m²], intermediate dose [6.5-11 mg/m²], high dose [12.5-14 mg/m²]) 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).

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.


D. J. C., J. A. d’A. and M. O. L. acknowledge CRUK, EPSRC, MRC and NIHR for funding the Cancer Imaging Centre (C1060/A10334) and NHS funding for the NIHR Biomedical Research Centre at ICR/RMH.