Introduction

OXi4503 (combretastatin A1 phosphate, CA1P: Oxigenex, 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 R2* 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 R2* measurements during the 1st 4 hours after OXi4503 administration. Changes observed in R2* 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/m2 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, 256×256 matrix) was used. T1-weighted DCE-MRI sequences (TE 4.7ms, TR 11ms, α 35˚, 256×256 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 [4] and a population arterial input function (Modified Fritz-Hansen [5]). Whole tumour DCE-MRI kinetic parameters (Ktrans, IAUGC60), and R2* were calculated.

Two MRI scans (DCE-MRI and R2*) were performed within 8 days prior to treatment to establish reproducibility. R2* 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].

Results

16 patients with 21 lesions were evaluable. R2* images of one patient is shown in Figure 1. Threshold values (n=1) were: R2* ±16.9%; Ktrans -16.04%; IAUGC60 ±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 R2* 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 Ktrans and/or IAUGC60 at >4hrs) there were less consistent group R2* changes although individual responding patients were seen in both groups. If both R2* and DCE-MRI parameters are used to assess OXi4503 activity (by significant increases in R2* and decreases in Ktrans/AUC60) 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 R2* shows significant VDA action within the 1st few hours after OXi4503. Both R2* and DCE-MRI show positive dose-response relationships. We were surprised to find a disconnection between temporal changes in R2* and static time point DCE-MRI change. This may be explained in part by the transient nature of the R2* change in DCE-MRI non-responders. In DCE-MRI responders, vascular collapse can empty blood vessels of red blood cells and therefore paradoxically lower R2*.

![Figure 1: Ovarian cancer (red circle) metastasis in right side pelvic lymph nodes R2* images at a) baseline, b) 1½ hrs, c) 3 hrs, and d) 4 hrs after OXi4503 infusion (8.5 mg/m2). After an initial increase in R2* there is a decrease noted by 4hrs.](image)

![Figure 2: Box plots for changes in R2* 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 R2* 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 R2* between the two groups. *p<0.05.](image)