Comparison of Arterial Spin Labelling and R2* as Predictive Response Biomarkers for Vascular Targeting Agents in Liver Metastases

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Introduction: Metastatic liver disease is the main cause of mortality in colorectal carcinoma (CRC) patients, with a 5 year survival rate of 40% following surgical resection of metastases. Surgery with curative intent is only possible in 10-20% of patients, demonstrating the need for alternative therapeutic approaches. The vascular disrupting agent OXi4503 is a compound that targets tumour vasculature and causes central tumour necrosis leaving a small viable rim of tumour cells. The acute (within 4 hours) accumulation of paramagnetic deoxyhaemoglobin resulting from vascular disruption has allowed R2* changes to be used as a biomarker of therapeutic effect. However, Arterial Spin Labelling (ASL) could offer an alternative quantifiable technique for assessing response, by measuring acute changes in tumour perfusion using wholly endogenous contrast mechanisms. The current study therefore aims to compare changes in R2* and ASL following OXi4503 treatment in a preclinical liver metastasis model.

Method: Animal model: The CRC cell line SW1222 was injected intrasplenically at a concentration of 1x10⁶ cells in 100 µl in serum free media into n=8 MF1 nu/nu mice. Cells were allowed to wash through to the liver for 1 minute followed by splenectomy. Solid tumour deposits developed within the liver at 4-6 weeks following surgery.

MRI: A 9.4T Agilent VNMRS 20cm horizontal bore system with a 39mm birdcage coil was used, with a warm air blower to maintain animal temperature. Respiratory gating (SA instruments, New York, USA) was used on all scans. Fast spin echo images were used to define a suitable imaging slice within the liver followed by a segmented FAIR Look-Locker ASL sequence with a single slice spoiled gradient readout. R2* values were assessed by a multi-gradient echo (MGE) image sequence covering the entire liver. FAIR Look-Locker ASL sequence parameters: 30 x 30 mm FOV, 128x128 matrix, TE: 1.18 ms, TI: 110 ms, TR: 2.3 ms, TR: 15 s, 50 inversion recovery readouts. Localised inversion thickness: 6 mm, imaging readout slice thickness: 1 mm, 4 lines per segmented acquisition. MGE sequence parameters: 8 echoes, TE=2 ms, echo spacing=2 ms, TR=280 ms; 128x128 matrix, 40x40mm FOV, 1 mm slice thickness.

Dosing: Cannulation of the tail vein was performed prior to baseline scans. Dosing of 40mg/kg via this remote i.v. line was performed in the scanner bore after baseline scans, and data acquired at 90 min post dose.

Data analysis: n=18 metastases were evaluated across the n=8 mice for ASL and n=12 were available for R2* analysis. Perfusion maps were generated using the Belle model, (T1omin=1.9 s, blood-tissue partition coefficient λ=0.95 ml/g min⁻¹) in MATLAB and R2* maps were created using IDL.

Results: A significant decrease was measured in ASL measurements of tumour perfusion at 90 mins following OXi4503 administration (P < 0.01, Mann-Whitney U test), with a mean change of -0.49 ml/g/min (-43%). A significant correlation was observed between baseline perfusion and the change in perfusion following therapy (Fig. 1A), suggesting that tumours better perfused at baseline responded better to the therapy. A significant increase in R2* was also measured (P < 0.01, Mann-Whitney U test), with a mean change of 0.010 ms⁻¹ (13%), but with no significant correlation with initial R2* (Fig.1B). There was no significant correlation between ASL and the R2* responses (Fig.1C).

Discussion: We were able to detect acute changes in tumour pathophysiology caused by OXi4503 with both ASL and R2*, with a significant decrease in mean perfusion and increase in R2*. This is consistent with the mechanism of action of VDAs: cessation of blood flow leads to a reduction in tumour perfusion and an increase in paramagnetic deoxygenated haemoglobin. Changes in R2* and perfusion were not correlated, indicating a complex relationship between changes in flow and accumulation of deoxyhaemoglobin, which may be specific to individual tumours. The data presented here shows that ASL can be a predictor of vascular targeting agent efficacy in liver metastases, suggesting that tumour deposits better perfused at baseline display a greater acute response. R2* response was not suggestive of any prognostic ability, but did respond positively. Given the mechanism of action of vascular disrupting agents, ASL provides response biomarkers that afford a less ambiguous interpretation than intrinsic susceptibility (R2*) measures. However, an approach combining the two may provide deeper insights in to the mechanics of tumour response in vivo, by relating flow changes to changes in blood oxygen saturation.

The detection of a variable response, even in tumour deposits within the same liver highlights the need for robust assessment of response within individual patients. ASL sequences are non-invasive and do not require the administration of a contrast agent and so could be performed serially, soon after therapy to inform on drug efficacy. Given that brain and kidney FAIR ASL is commonplace in clinical scanners we anticipate a translation of hepatic ASL should be straightforward. Further work will characterise the response at later time points post OXi4503 and assess changes in perfusion and R2* in other tumour lines in preclinical metastases models.

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