Use of Dynamic Contrast-Enhanced MRI to Predict Drug Uptake in Patients

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Introduction:

Effectiveness of many pharmaceuticals is limited by poor delivery to the target tissue. Patients often undergo contrast-enhanced MRI as part of their clinical management. We investigate here whether dynamic contrast-enhanced MRI can be used to predict subsequent drug delivery. The drug we chose as our model is SR4554, a diagnostic agent in phase 1 clinical trials that was designed by Workman and colleagues to be detectable with ^{19}F Magnetic Resonance Spectroscopy, and to be retained in regions of tissue hypoxia (1).

Methods

Study overview. Patients with a range of large or superficial tumours were selected. Diagnostic and dynamic contrast-enhanced MRI was performed a few days prior to the administration of SR4554. SR4554 was given as an infusion over 1 hour. ^{19}F MRS measurements were performed immediately after infusion (MRS#1), and at 16 hours (MRS#2). The ratio of signals, MRS#2 / MRS#1, gives an indication of retention of SR4554 in the tumour. Plasma samples were obtained before and after each spectroscopy measurement so that plasma concentrations could be calculated. The study described here investigated whether, in 7 patients for which identical RF coils were used, a correlation existed between vascular parameters derived from the dynamic MRI data, and drug delivery as measured by the first ^{19}F MRS measurements.

MR Measurements. MR measurements used a 1.5T Siemens Vision system. DCE-MRI data were acquired using the Siemens body array, head and neck, or flex rf receiver coils. Following acquisition of T_1-weighted and T_2-weighted anatomical images a single slice was selected through the tumour. A double dose bolus of Gd-DPTA (Magnevist) was injected at 5ml/s 8 s after the start of acquisition. Contrast agent dynamics were followed using 288 sequential T_1-weighted and T_2*-weighted double echo images acquired every second (TE = 6.8ms and 18.0ms, TR=30ms; matrix = 128x128 [(2)]).

^{19}F MRS measurements were performed using 5, 10 or 16 cm dual resonant ^{1}H/^{19}F custom-built surface coils[4] immediately after infusion of SR4554. Following tumour localisation with TruFISP imaging sequence, and shimming, ^{19}F MRS signals were acquired using a pulse-acquire sequence (TR = 1s; NS = 512) and 3D spectroscopic imaging (8x8x8 grid; TR = 2; NS = 2 or 4). All MRS acquisition used a 1.28 ms adiabatic tanh rf pulse to achieve uniform excitation.

Analysis. Post-processing of the dynamic data allowed calculation in each pixel of the contrast agent transfer constant (K^{trans}), volume fraction(v_e) of the extracellular extravascular space (EES), relative blood volume (rBV) and mean transit time (MTT) [2].The localised MRS#1 signal intensity was normalised for the dose of the SR4554 infused, the size of the MRS voxel and distance from the coil. A Pearson's correlation coefficient was computed between this and the median value of the kinetic parameters over an ROI corresponding to the MRS voxel size and location. DCE-MRI parameters correlations with retention index were also computed.

Results and Discussion:

Dynamic Parameter	Corr coefficient, r
v_e	0.828 (p=0.022)
K^{trans}	0.741 (p=0.057)
k_{ep}	0.582 (p=0.17)
rBF	0.910 (p=0.044)
rBV	0.812 (p=0.026)
MTT	0.179 (p=0.7)

Table 1. Correlation coefficients for vascular parameters compared with uptake of SR4554

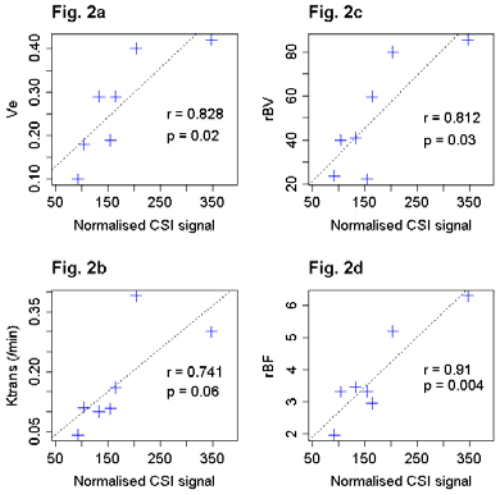

Figure 2. Correlations between dynamic parameters and MRS signals

The correlation coefficients for the initial localised ^{19}F MRS from SR4554 with the dynamic parameters derived from the dynamic MRI are summarised in Table 1 and Figure 2. There is clearly a good correlation between v_e, $K^{trans,}$ rBV and rBF with SR4554 uptake over a 3-fold range. A poor correlation is seen with k_{ep} and none with MTT. A related pre-clinical study performed in experimental tumours (3) showed good correspondence between uptake of the contrast agent and that of a therapeutic agent, but the other vascular parameters were not presented. The previous study had better spatial resolution for the MRS than was possible in our clinical study but the close correlations observed show that this is not essential to demonstrate the correspondence between contrast and drug delivery.

Conclusion:

Vascular parameters derived from dynamic contrast-enhanced MRI give a good prediction of drug delivery to the tumour.

References: (1) BM Seddon Clin Canc Res. 9:5101 (2003); EO Aboagye Canc Res 57:3314 (1997) (2) JA d'Arcy NMR Biomedicine 15:174 (2002) (3) D Artemov Canc Res. 61:3039 (2001) (4) DJ Collins ISMRM 2000 p1417

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