DCE-MRI in patients with mRCC: pilot study investigating possible biomarkers of antiangiogenic therapy

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Introduction

This study investigated the use of DCE-MRI pharmacodynamic biomarkers as early indicators of the activity of the antiangiogenic drug bevacizumab when used in patients with metastatic renal cell carcinoma (mRCC). The DCE-MRI investigation was carried out as part of a larger trial involving MR-DWI and ^{18}F-FMISO PET-CT imaging post-treatment.

Methods

The study received approval from the local ethics committee. To date, 10 patients with histologically proven mRCC have been recruited, each having giving written consent. Each patient received 3 infusions of bevacizmub (10 mg/kg body mass) at 2-week intervals. The patients were scheduled to have 4 identical MR examinations on a GE 1.5T scanner (Signa HDx, GEHC, Waukesha, WI): two base-line examinations were performed pre-treatment (visits 'b1' & 'b2'); post-treatment, one examination was performed 4 hours after the first infusion of bevacizumab (visit '4h') and the final examination was on the third day following infusion (visit '72h'). At each MRI examination, 0.1 mmol/kg of Gd-DOTA (Dotarem, Guerbet, S.A.) was administered by power injector. The dynamic series was obtained using a 3-D fast spoiled gradient echo sequence (TR/TE 4.0/1.7 ms; α = 18°; 0.7 NEX; FOV 35-40 cm; matrix 160 x 160 x 14; ASSET x 2), with a temporal resolution of ~3.1 seconds over a time-frame of ~10 minutes. T_1 mapping data was collected with a series of single measurements from a similar sequence (without ASSET) repeated across a set of multiple flip angles (MFA) (1°, 3°, 5°, 10°, 15°, 20°).

At the time of writing, 7 patients' data-sets have been analysed, one set including only the pre-treatment scans. The dynamic images were aligned using custom software which employed a non-linear registration algorithm using mutual information **[1]**. Tumour outlines were drawn on each slice by a skilled operator using custom software. Signal data was extracted across the dynamic series on a pixel-by-pixel basis within the drawn ROIs, and signal to [Gd] conversion was achieved using the standard spoiled gradient echo and relaxivity equations. The pixel T_{10} values used in this conversion process were read from T_1 maps calculated from the MFA data. The 'extended Tofts' pharmacokinetic model **[2]** was fitted by custom software to the [Gd] enhancement curves using a model arterial input function, based on measurements by Fritz-Hansen **[3]** and by Weinmann **[4]**, to yield parameter maps within the tumour ROIs for K^{trans}, k_{ep}, v_e and v_p. IAUGC90 ('initial area under the [Gd] curve to 90 seconds') maps were also generated, as well as maps indicating model-fitting convergence categories.

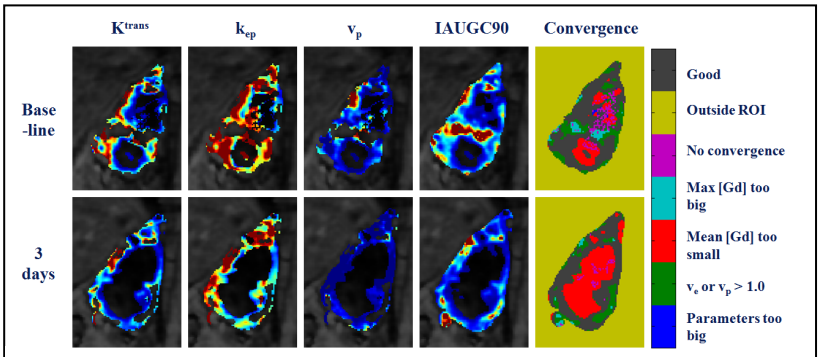

Fig. 1: Sample tumour DCE parameter maps: (top row) base-line exam (visit 'b2'); (bottom row) 3-days post-treatment (visit '72h')

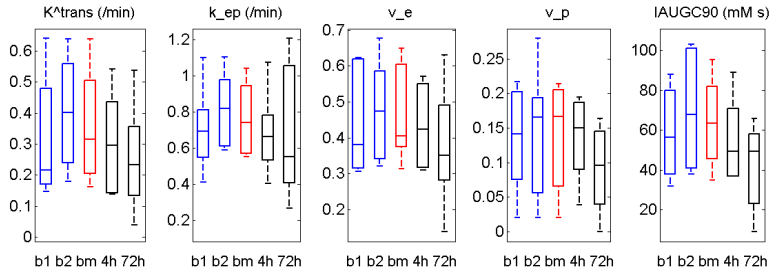

Fig. 2: Box-plots of median parameter values across n=6 patients (baseline visits 'b1', 'b2' in blue, 'bm' = mean (b1,b2) in red, visits '4h', '72h' post-treatment in black)

p-values	4h & bm	72h & bm
K^{trans}	0.083	0.040*
k_{ep}	0.069	0.400
v_e	0.518	0.092
v_p	0.691	0.031*
IAUGC90	0.035*	0.007*

Table 1: p-values from paired t-test: 4h & bm=mean (b1,b2) and 72h & bm (n = 6)

The generated parameter maps were subjected to histogram analysis, to yield mean, median and percentile tables. The averages were taken over all slices and included all tumour voxels for which either the modelling process converged satisfactorily or else the mean of the [Gd] curve was less than a defined threshold (0.01 mM). The latter condition indicated no discernible Gd uptake in the voxel: the perfusion parameters indicating blood flow for these voxels were set to zero before being entered into the averaging process. This process ensured that the extent of any hypo-perfused central region of a tumour was represented in the averaged results.

Results

Sample parameter maps from a tumour with a non-enhancing central region are shown in Figure 1. The convergence map indicates the increase in the number of non-enhancing pixels (shown in red) 3 days after treatment. Box-plots of the parameter results for the 6 patients who underwent 4 examinations each are shown in Figure 2. Paired t-tests were performed on the following sets of paired data (values compared were the median of the specified parameter within the tumour): visit '4h' with the mean of baseline measurements, 'bm' = mean('b1','b2'); and visit '72h' with the same baseline mean measurements. (The differences were found to be approximately normally distributed using the Shapiro-Wilks test, allowing t-tests to be applied.) The p-values from these two-tailed t-tests are given in Table 1. Employing a significance level of 5%, the p-values are consistent with the 3-days post-treatment visit ('72h') differing from the mean of the baseline in K^{trans}, v_p and IAUGC90. Immediately post-treatment (visit '4h') there is a significant reduction in IAUGC90 but not in any other parameter. Individual data-sets show a reduction in K^{trans}, v_p and IAUGC90 values between mean pre-treatment ('bm') and 3-day post-treatment ('72h') in 5 out of 6 patients.

Conclusion

The reductions in median tumour K^{trans}, v_p and IAUGC90 values 3-days post-treatment are consistent with the hypothesis of a reduction in tumour vascularity following treatment with the antiangiogenic agent bevacizumab. It is of interest that the IAUGC90 index, derived from a less sophisticated test not dependent upon a kinetic model, also shows this effect just 4 hours after treatment. As the study progresses, an attempt will be made to correlate these results with patient outcome.

References

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