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 18F-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 given written consent. Each patient received 3 infusions of bevacizumab (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 baseline 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, each are shown in Figure 2.

Results

Each patient received 3 infusions of bevacizumab (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 baseline 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. T1 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 T1 and T2p values used in this conversion process were read from T1 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 Ktrans, kep, vp, and IAUGC90 (‘initial area under the [Gd] curve to 90 seconds’) maps were also generated, as well as maps indicating model-fitting convergence categories.

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 p-values from these two-tailed t-tests 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.

Conclusion

The reductions in median tumour Ktrans, vp, 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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Fig. 1: Sample tumour DCE-MRI parameter maps: (top row) base-line exam (visit ‘b2’), 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)

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