MR measurements of pre-treatment tumour perfusion appear to correlate with response to dexamethasone in patients with gliobastoma multiforme.

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Introduction: MRI-based measurements of brain tumour perfusion and permeability have been shown to correlate with tumour grade and there is growing interest in using these parameters as markers of treatment response [1,2]. In this work, we investigate whether pre-treatment measurements of tumour perfusion correlate with subsequent response to dexamethasone treatment in high grade glioma.

Methods: Nine patients with newly diagnosed WHO Grade IV glioblastoma were recruited into the study. The recruitment criteria were: 1) had not begun steroid treatment, 2) had no prior radiotherapy or chemotherapy and 3) no contraindications to MRI. Dynamic contrast enhanced MRI (DCE-MRI) was performed using a 3D FSPGR sequence (TR / TE = 8.0 / 3.3 ms, 36 axial slices, 3 mm thick, 256 × 256 matrix, 240 × 240 mm FOV). The sequence was acquired with flip angles of 2º and 12º before contrast and then the 12º acquisition repeated 10 times following administration of 20ml gadopentetate dimeglumine (Magnevist, Berlex Laboratories, NJ). Following this, dynamic susceptibility contrast MRI (DSC-MRI) was performed using 34 consecutive acquisitions of single-shot, gradient echo, echo planar imaging (TR / TE = 2500 / 30 ms, 15 axial slices, 5 mm thick, 128 × 128 matrix, 240 × 240 mm FOV) with a second dose of contrast agent administered after 10s. The DCE- and DSC-MRI protocols were repeated before and at 48 - 72h after initiation of dexamethasone treatment at 16mg/day. Images were transferred in DICOM format to a standard PC workstation and processed using in-house software written in C. DCE-MRI analysis consisted firstly of calculating pre-contrast T_1, which allowed for contrast agent concentration to be estimated at each time point [2]. The concentration-time curves were then fitted with a pharmacokinetic model, as described previously [2], allowing for estimation of K^{trans} and v_e as well as the area under the concentration-time curve *CA*. DSC-MRI analysis involved estimation of contrast agent concentration using standard techniques [3], followed by gamma-variate curve fitting and calculation of relative perfusion parameters *rCBV*, *rMTT* and *rCBF* from the area under the fitted curve, first moment of the curve and the ratio of the former two measures, respectively. Each of the perfusion parameters were normalized by their respective measure in normal-appearing white matter and these were denoted as CBV_n, MTT_n and CBF_n. Regions of interest encompassing the whole of the enhancing tumour were measured for each of the parameters and the percentage difference between the pre- and post-treatment images was noted for each parameter. The percentage difference was calculated using $\Delta A = 100 \times (A_{PRE} - A_{POST}) / A_{PRE}$, where A represents K^{trans}, v_e or *CA* and the subscripts *pre* and *post* indicate the pre- and post-treatment measurements, respectively. Regression analysis was then performed to correlate the pre-treatment tumour perfusion measured by CBV_n, CBF_n and MTT_n with ΔK^{trans}, Δv_e and ΔCA.

Results: ΔCA was strongly correlated with both the pre-treatment CBF_n ($R^2 = 0.90$, $p < 0.001$) and CBV_n ($R^2 = 0.76$, $p = 0.002$). *CA* can be considered to have components relating to both K^{trans} and v_e and it was found that ΔK^{trans} was poorly correlated with CBF_n ($R^2 = 0.0002$, $p = 0.97$) and CBV_n ($R^2 = 0.012$, $p = 0.78$), while Δv_e was strongly correlated with both CBF_n ($R^2 = 0.80$, $p = 0.001$) and CBV_n ($R^2 = 0.64$, $p = 0.009$). In contrast, pre-treatment MTT_n did not correlate with ΔK^{trans} ($R^2 = 0.13$, $p = 0.34$), Δv_e ($R^2 = 0.04$, $p = 0.59$), or ΔCA ($R^2 = 0.08$, $p = 0.45$). These correlations are represented graphically for ΔCA in Fig.1 and representative images of pre-treatment *rCBF*, pre- and post-treatment *CA* are shown in Fig.2.

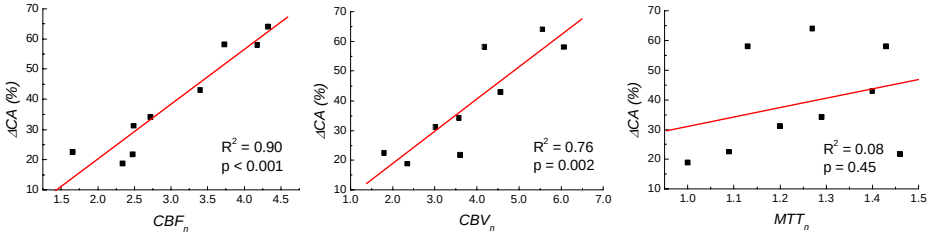

Figure 1: Correlations between pre-treatment CBF_n, CBV_n and MTT_n and post-treatment percentage change in *CA* (ΔCA).

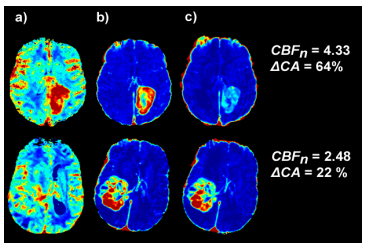

Figure 2: Representative images from two patients showing pre-treatment *rCBF* (a), pre-treatment *CA* (b) and post-treatment *CA* (c).

Discussion: It has been previously demonstrated that tumour K^{trans} and v_e are reduced following dexamethasone treatment [2]. The results presented here suggest that the degree of reduction in v_e is strongly correlated with the pre-treatment tumour perfusion as measured by CBF_n and CBV_n. We hypothesise that a higher tumoural CBF and CBV will provide a greater supply of dexamethasone to the tumour, resulting in a greater treatment effect. We do not believe that the effect is simply due to patients with higher CBV and CBF initially having more abnormal vasculature because no significant correlation was observed between pre-treatment K^{trans}, v_e or *CA* and their respective post-treatment changes. It is interesting to note that there is no correlation between pre-treatment perfusion and change in K^{trans}, despite K^{trans} being reduced post-treatment [2]. This suggests that dexamethasone may act to reduce the extravascular extracellular space via another mechanism as well as a consequence of reducing tumour permeability. The results suggest that measurements of tumour perfusion may be useful for predicting treatment response and would therefore be worth investigating in newer therapies (e.g. [1]), particularly those with undesirable side-effects, where if the present findings were corroborated, treatment could be targeted at patients with well-perfused tumours.

Conclusion: MRI-based measurements of pre-treatment tumour perfusion appear to predict the response to dexamethasone as measured by DCE-MRI. A larger study is required to validate these findings, particularly in relation to clinical response, but these results suggest that it would be worthwhile investigating pre-treatment perfusion measures when studying other treatments.

References: [1] Batchelor TT, et al. *Cancer Cell* 2007;11:83-95. [2] Armitage PA, et al. *Magn Reson Imaging* 2007;25:303-310. [3] Ostergaard L, et al. *Magn Reson Med* 1996;36:726-736.

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