Short report

Pretreatment tumoural perfusion correlates with an imaging-based response to dexamethasone in patients with glioblastoma multiforme

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ABSTRACT

Imaging-based markers of treatment response are increasingly being used in studies of brain-tumour therapies, for evaluating novel treatments and further understanding of existing therapies. An ultimate goal of these studies is to identify pre- or early-stage treatment imaging biomarkers that enable prediction of subsequent treatment response. We hypothesised that pretreatment MRI-based measurements of tumoural perfusion may provide a suitable imaging-based biomarker for prediction of subsequent treatment response and evaluated this in a group of nine high-grade glioma patients undergoing dexamethasone treatment. A strong positive correlation was observed between tumoural blood flow (R²=0.90, p<0.001) and tumoural blood volume (R²=0.76, p=0.002), and subsequent treatment response as measured by alterations in tumour leakage properties. These preliminary results indicate that measurements of tumoural perfusion may provide useful imaging biomarkers for predicting treatment response to dexamethasone and would therefore also be worth evaluating in newer emerging therapies.

INTRODUCTION

Dexamethasone has been used for the management of intracranial tumours since early clinical observations of its efficacy in these patients.1 However, despite a generally accepted rapid and beneficial clinical effect, there is still a significant amount of variability in the degree of response between patients.2 This is, perhaps, unsurprising given the highly variable and heterogeneous nature of the tumour microenvironment and vascular properties. Imaging techniques offer a mechanism for non-invasively characterising the tumour microenvironment, potentially leading to identification of imaging biomarkers for characterising and predicting treatment response.

MRI techniques have been developed to enable measurement of parameters such as diffusion, perfusion, permeability, pH, and water content.3–7 These parameters provide useful information about the tumour microenvironment and have been studied extensively in intracranial tumours as potential markers of treatment response.7–12 However, to date, no study has been performed to identify if these biomarkers, when measured pretreatment, can be used to predict subsequent response. As a first step towards this, we investigated whether MRI-derived biomarkers, measured pretreatment, correlate with subsequent response to treatment at 48–72 h following initiation. In particular, we hypothesised that tumoural perfusion could be a useful biomarker for predicting treatment response due to dexamethasone, since tumoural blood supply may influence dexamethasone distribution into tumoural tissue. To investigate this, MRI measurements of perfusion, permeability and diffusion were performed in a group of high-grade glioma patients before and 48–72 h following initiation of dexamethasone therapy. Pretreatment perfusion values were correlated with subsequent image-based responses to treatment.

MATERIALS AND METHODS

Patients

Nine consecutive patients with radiologically diagnosed WHO Grade IV glioblastoma multiforme (later confirmed by histology) were recruited into the study (mean age 63±9 years, five females). Patients were recruited if they had (1) no MR contraindications, (2) not begun steroid treatment and (3) no prior radiotherapy or chemotherapy. Following initial imaging, patients underwent dexamethasone therapy (16 mg/day PO) before undergoing follow-up imaging 48–72 h later. The local ethics committee approved the study, and written informed consent was obtained from all patients.

Imaging measurements

All imaging was performed on a GE Signa LX 1.5T scanner (General Electric, Milwaukee, Wisconsin) and consisted of clinical imaging, dynamic susceptibility contrast MRI (DSC-MRI), dynamic contrast-enhanced MRI (DCE-MRI) and diffusion tensor MRI (DT-MRI). Each of the DCE- and DSC-MRI protocols was performed using separate 20 ml injections of gadopentetate dimeglumine (Magnevist, Berlex Laboratories, Wayne, New Jersey) into the antecubital fossa vein at 5 ml/s using an MR-compatible power injector (Medrad, Indianola, Pennsylvania). Full details of the MRI protocol have been described elsewhere.11 Standard post-processing techniques involving gamma-variate curve fitting were applied to the DSC-MRI data to obtain maps of relative perfusion parameters.4 The regional cerebral blood volume (rCBV) was calculated from the area under the concentration–time curve, the regional mean transit time (rMTT) from the first moment of the curve and the regional cerebral blood flow (rCBF) from the ratio of the first two. Concentration–time curves were estimated from the DCE-MRI acquisition using a previously described model15 and maps of the area under the concentration–time curve (CA), volume transfer constant (Ktrans), and extravascular extracellular space volume fraction (ve) were obtained by fitting...
a pharmacokinetic model to the concentration-time curves. From a biological perspective, CA indicates the total amount of contrast agent accumulating during the course of the imaging period in each voxel, and $K_{\text{trans}}$ is a proxy for the endothelial permeability (actually the permeability − surface area product per unit volume of tissue). The DT-MRI data were used to calculate the mean diffusivity ($D_{\text{av}}$) as the average of the diagonal elements of the diffusion tensor. This parameter measures the mobility of water and therefore indicates how free or restricted the local water environment is. Region-of-interest measurements were taken of rCBV, rCBF, rMTT, CA, $K_{\text{trans}}$ and $v_e$ in enhancing tumour (identified on postcontrast T1-weighted imaging) and $D_{\text{av}}$ in oedema, both pre- and post-treatment, using the methodology described previously. Measurements of tumoural rCBV, rCBF and rMTT were divided by corresponding measurements from contralateral normal-appearing white matter to give CBVt, MTTt and CBFt, respectively. Therefore, for example, CBVt represents the proportion by which the tumoural rCBV is elevated above that of normal-appearing white matter, such that a CBVt of 2 would indicate that tumoural blood volume is twice that of normal-appearing white matter. Pretreatment measurements of CBVt, CBFt and MTTt were correlated with the percentage pre- to post-treatment reduction in tumour CA, $K_{\text{trans}}$ and oedema $D_{\text{av}}$ ($\Delta$CA, $\Delta K_{\text{trans}}$, $\Delta v_e$ and $\Delta D_{\text{av}}$) using linear regression analysis. The percentage change in these parameters was taken as surrogate markers of treatment response, as they represent reduced tumour leakage or reduced oedema diffusivity, both of which are believed to be factors associated with clinical improvement.

**RESULTS**

Pretreatment measurements of CBVt were strongly correlated with post-treatment reductions $\Delta$CA ($R^2=0.76$, $p=0.02$) and $\Delta v_e$ ($R^2=0.64$, $p=0.009$), but not with $\Delta K_{\text{trans}}$ ($R^2=0.01$, $p=0.78$). Similarly, CBFt was also strongly correlated with post-treatment reductions $\Delta$CA ($R^2=0.90$, $p<0.001$) and $\Delta v_e$ ($R^2=0.80$, $p=0.001$), but not with $\Delta K_{\text{trans}}$ ($R^2=0.0002$, $p=0.97$). In contrast, MTTt did not correlate with $\Delta$CA ($R^2=0.06$, $p=0.45$), $\Delta v_e$ ($R^2=0.04$, $p=0.59$) or $\Delta K_{\text{trans}}$ ($R^2=0.13$, $p=0.34$). Both CBVt and CBFt showed moderate but statistically insignificant correlations with $\Delta D_{\text{av}}$ ($R^2=0.26$, $p=0.16$ and $R^2=0.42$, $p=0.06$, respectively), while MTTt showed no correlation with $\Delta D_{\text{av}}$ ($R^2=0.005$, $p=0.86$). Figure 1 illustrates typical examples from four subjects, illustrating how initial rCBF appearance compares with CA pre- and post-treatment, along with graphs illustrating the correlations between these parameters for all nine patients.

![Figure 1](http://jnnp.bmj.com/)

**Figure 1**  Example graphs illustrating the correlation between $\Delta$CA and CBFt for all nine patients (upper left) and $\Delta$CA and CBVt (lower left). Also shown are images illustrating the striking visual correlation between pretreatment regional cerebral blood volume (rCBV) and pre-/post-treatment change in CA from four typical example cases with a range of different treatment responses (right). Delta CA is the percentage pre- to post-treatment change in CA where CA is the area under the concentration-time curve of the DCE-MRI analysis. CBFt is the pre-treatment regional cerebral blood flow (rCBF) value measured in tumoural tissue and normalised to its equivalent normal appearing white matter value. CBVt is the pre-treatment regional cerebral blood volume (rCBV) value measured in tumoural tissue and normalised to its equivalent normal appearing white matter value.
DISCUSSION

In addition to the expected reduction in tumour $\Delta$CA, $\Delta$K$_{trans}$, $\Delta$V$_e$ and oedema $\Delta$D$_{av}$ following dexamethasone therapy as identified in previous work, the results demonstrate a strong correlation between pretreatment CBVt and CBFt, and subsequent treatment response, as measured by $\Delta$CA and $\Delta$V$_e$. This suggests that the supply of blood to the tumour is an important factor in determining response to dexamethasone, where the rate of blood supply CBFt appears to be the critical factor in determining dexamethasone response. While this correlation may be expected for a drug like dexamethasone, we believe this to be the first time this has been measured and demonstrated in a quantitative way.

Despite pretreatment tumour perfusion being strongly correlated with $\Delta$CA and $\Delta$V$_e$, it does not correlate with $\Delta$K$_{trans}$, although this is known to be reduced post-treatment. As CA is a function of both K$_{trans}$ and V$_e$ (as both of these parameters determine the area under the concentration–time curve), the results indicate that the correlation between pretreatment perfusion and $\Delta$CA arises from the correlation with $\Delta$V$_e$. This suggests that dexamethasone may act to reduce the extravascular extracellular space, as well as a consequence of reducing tumour permeability. A further possibility is that the measurement of K$_{trans}$ may be prone to error with the current acquisition, due to permeability. A further possibility is that the measurement of the enhancing tumour region. Oedema resolution is believed to correlate imaging-based measurements of oedema resolution and oedema changes, or between initial CBFt and CBVt and their respective $\Delta$D$_{av}$ was the only biomarker to be elucidated by quantitative diffusion tensor MRI.

In previous work, the results demonstrate a strong correlation between pretreatment CA and $\Delta$V$_e$, it does not correlate with $\Delta$K$_{trans}$, while investigating as potential biomarkers of treatment effect relationship of CA and perfusion imaging. In conclusion, a strong correlation has been found between pretreatment MRI measurements of tumour perfusion and subsequent assessment of dexamethasone response. Larger studies are clearly required to validate these findings and their relevance to clinical function. These preliminary results suggest that pretreatment perfusion measurements would be worth while investigating as potential biomarkers of treatment response with new therapies.

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