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CLINICAL INVESTIGATION **Brain**

POTENTIAL FOR DIFFERENTIATION OF PSEUDOPROGRESSION FROM TRUE TUMOR PROGRESSION WITH DYNAMIC SUSCEPTIBILITY-WEIGHTED CONTRAST-ENHANCED MAGNETIC RESONANCE IMAGING USING FERUMOXYTOL VS. GADOTERIDOL: A PILOT STUDY

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Purpose: We evaluated dynamic susceptibility-weighted contrast-enhanced magnetic resonance imaging (DSC-MRI) using gadoteridol in comparison to the iron oxide nanoparticle blood pool agent, ferumoxytol, in patients with glioblastoma multiforme (GBM) who received standard radiochemotherapy (RCT).

Methods and Materials: Fourteen patients with GBM received standard RCT and underwent 19 MRI sessions that included DSC-MRI acquisitions with gadoteridol on Day 1 and ferumoxytol on Day 2. Relative cerebral blood volume (rCBV) values were calculated from DSC data obtained from each contrast agent. T1-weighted acquisition post-gadoteridol administration was used to identify enhancing regions.

Results: In seven MRI sessions of clinically presumptive active tumor, gadoteridol-DSC showed low rCBV in three and high rCBV in four, whereas ferumoxytol-DSC showed high rCBV in all seven sessions ($p = 0.002$). After RCT, seven MRI sessions showed increased gadoteridol contrast enhancement on T1-weighted scans coupled with low rCBV without significant differences between contrast agents ($p = 0.9$). Based on post-gadoteridol T1-weighted scans, DSC-MRI, and clinical presentation, four patterns of response to RCT were observed: regression, pseudoprogression, true progression, and mixed response.

Conclusion: We conclude that DSC-MRI with a blood pool agent such as ferumoxytol may provide a better monitor of tumor rCBV than DSC-MRI with gadoteridol. Lesions demonstrating increased enhancement on T1-weighted MRI coupled with low ferumoxytol rCBV are likely exhibiting pseudoprogression, whereas high rCBV with ferumoxytol is a better marker than gadoteridol for determining active tumor. These interesting pilot observations suggest that ferumoxytol may differentiate tumor progression from pseudoprogression and warrant further investigation. © 2011 Elsevier Inc.

Blood-brain barrier, Dynamic susceptibility-weighted contrast-enhanced magnetic resonance imaging, Glioblastoma multiforme, Pseudoprogression, Radiochemotherapy.

INTRODUCTION

The term *pseudoprogression* is used to describe the phenomenon of subacute imaging changes in human glioma subsequent to radiochemotherapy (RCT) with or without associated clinical sequelae (1). Increased or new enhancement after RCT can reflect pseudoprogression, which can occur up to 6 months after treatment (2, 3), as well as true tumor progression, which can happen at any time after treatment. However, patients with pseudoprogression, unlike true tumor progression, recover or stabilize spontaneously, generally without any changes in their treatment paradigm (1). The etiology of pseudoprogression is thought to be due to vascular and oligodendroglial injury leading to inflammation and increased permeability of the blood-brain barrier (BBB)

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(4–6). Varying incidences of pseudoprogression are reported, but recent reports (7, 8) estimate it to be as high as 30% within the first few months after RCT. Distinguishing true tumor progression from pseudoprogression is crucial in disease management decisions. Standard T2-weighted and gadolinium-based contrast agent (GBCA)-enhanced T1-weighted magnetic resonance imaging (MRI) sequences cannot reliably distinguish true tumor progression and pseudoprogression (1, 7).

Dynamic susceptibility-weighted contrast-enhanced MRI (DSC-MRI, also referred to as perfusion-weighted imaging) measurement of relative cerebral blood volume (rCBV) has been used for glioma grading (9–12), assessment of glioma patient prognosis (12–16) and differentiation of recurrent tumor from radiation necrosis (17–19). High rCBV indicates active neovascularization and viable tumor (15). Accurate measurement of rCBV using standard DSC modeling approaches relies on intravascular localization of contrast agent in the tissue of interest. This condition is compromised by the leaky BBB present within malignant brain tumors, especially after RCT. Rapid extravasation of GBCA from blood vessels into the extravascular/extracellular space can confound the rCBV estimation obtained using DSC-MRI (20). Therefore, DSC-MRI using GBCA can falsely estimate low rCBV in some patients with progressive disease (18, 19).

Ferumoxytol, an ultrasmall superparamagnetic iron oxide nanoparticle approved by the Food and Drug administration for iron replacement therapy, is gaining utility in brain imaging (21). Ferumoxytol acts as a blood-pool agent in the short term (minutes to hours), so its vascular localization is not compromised by the leaky BBB in tumors (22). The differences in vascular leakage between ferumoxytol and GBCA may be accentuated by antiangiogenesis agents that can markedly affect tumor permeability to GBCA (22). Additionally, unlike other iron oxide nanoparticle contrast agents, ferumoxytol is safe when given as a fast bolus injection (23). For these reasons, we hypothesized that ferumoxytol has the potential to measure rCBV more accurately than GBCA. In this report, we present our preliminary results comparing rCBV estimated from DSC-MRI with ferumoxytol vs. GBCA in patients with glioblastoma multiforme (GBM) for the potential of differentiating pseudoprogression from true tumor progression.

METHODS AND MATERIALS

Between April 2007 and December 2008, 14 patients with GBM were prospectively studied in one of three different research imaging protocols sponsored by the National Cancer Institute and approved by the Oregon Health & Science University institutional review board. Protocols 2753, 2864, and 1562 all compare anatomical and dynamic MRI using GBCA vs. ferumoxytol. Informed written consent was obtained from all patients.

Inclusion criteria for this analysis included histologically proven GBM (World Health Organization classification, Grade IV), standard postsurgical treatment—radiotherapy combined with concomitant and adjuvant treatment with temozolomide, and increased or new enhancement on conventional GBCA-enhanced T1-weighted MRI post-RCT.

Four patients on protocol #2753 underwent DSC imaging twice, first after surgery but before RCT when residual tumor was detected and second within a week after completion of RCT. Another patient underwent DSC-MRI twice after completion of RCT (2 and 28 months) because of increased enhancement on conventional MRI. The remaining patients had DSC-MRI once (only after completion of RCT) and were entered in the study because of increased/new enhancement on post-RCT follow-up MRI. Patient information is provided in Table 1. As shown, in the majority of cases, rCBV estimation was performed within 1 month after the increase of GBCA enhancement seen after completion of RCT.

MRI

The 14 patients underwent a total of 19 MRI sessions. Each session consisted of two consecutive days of MRI scanning. On the first day, precontrast and postcontrast T1-weighted images and DSC-MRI were acquired using gadoteridol gadolinium (III) chelate (ProHance, Bracco Diagnostic Inc., Princeton, NJ). On the following day, the same MRI sequences were acquired using ferumoxytol (provided by AMAG Pharmaceuticals, Inc., Cambridge, MA).

Eighteen of 19 MRI sessions were conducted using a 3T whole-body MRI system (TIM TRIO, Siemens, Erlangen, Germany) with a body RF coil transmit and 12-channel phased-array head radiofrequency receiver coil. One MRI session was performed using a 7T MR system (MAGNETOM 7 T, Siemens) equipped with an eight-channel phased array transmit/receive RF head coil (Rapid Biomedical Rimpar GMBH, Germany).

For DSC-MRI, dynamic T2*-weighted images were acquired using a gradient-echo echo-planar imaging pulse sequence (repetition time = 1500 ms, echo time = 20 ms, flip angle 45°, field of view 192 × 192 mm, matrix 64 × 64, and 27 interleaved slices (3T) or 13 slices (7T) with 3 mm thickness and 0.9 mm gap). After an initial baseline period of seven series of 27 image slices (11 s), a rapid bolus of contrast agent was administered intravenously using a power injector (Spectris Solaris - MEDRAD Inc., PA) through an 18-gauge intravenous line at a rate of 3 mL/s, followed immediately by 20 mL of saline flush at the same rate. DSC data collection continued for 90 series (2 min, 21 s). Gadoteridol was injected at a dose of 0.1 mmol/kg of body weight. Ferumoxytol was given as a dose of either 2 mg/kg (protocol #2753) 1 mg/kg (protocol #2864), or in a constant volume of 2.5 mL diluted with 2.5 mL saline (75 mg) regardless of body weight (protocol #1562).

T1-weighted images were collected pre and 20 minutes post-gadoteridol using a magnetization prepared rapid gradient read out (MPRAGE echo time 2.7/repetition time 2300/inversion time 900).

Imaging analysis

All first-pass DSC-MRI data were processed using Lupe (Lund, Sweden) perfusion image analysis software. The arterial input function was determined from the middle cerebral artery contralateral to the enhancing lesion. Color-coded rCBV maps were created on a voxel-wise basis uncorrected for contrast leakage, and were overlaid onto the post-gadoteridol T1-weighted images. Within the enhancing lesion, a single voxel (3 × 3 × 3 mm) region of interest (ROI) with the highest rCBV value on the ferumoxytol-rCBV parametric map and the same ROI on the gadoteridol-rCBV parametric map were analyzed using ImageJ software (http://rsb.info.nih.gov/ij). Areas depicting major vessels were excluded from ROIs. The rCBV values were calculated as the ratio of highest lesion blood volume to normal appearing contralateral white matter blood volume