Early Cerebral Blood Volume Changes Predict Progression After Convection-Enhanced Delivery of Topotecan for Recurrent Malignant Glioma

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■ OBJECTIVE: **To assess whether early changes in enhancing tumor volume (eTV) and relative cerebral blood volume (rCBV) 1 month after convection-enhanced delivery of topotecan in patients with recurrent malignant glioma correlated with 6-month disease progression status.**

■ METHODS: **Sixteen patients were enrolled in a Phase Ib trial of convection-enhanced delivery of topotecan for recurrent malignant glioma. Each patient was evaluated with serial follow-up magnetic resonance imaging at baseline and at 4- to 8-week intervals. Changes at 1 month compared with baseline in eTV and rCBV were evaluated as potential predictors of 6-month progression status, classified as either progressive disease or nonprogressive disease. Relationships between percent changes in eTV and rCBV at 1 month with the probability of progressive disease at 6 months were estimated by the use of logistic regression analysis. Receiver operating characteristic curves for varying percent change thresholds in eTV and rCBV were evaluated by the use of 6-month progressive disease as the reference.**

■ RESULTS: **There was a significant difference in the percent change in rCBV at 1 month in patients with progressive disease compared with those with nonprogressive disease at 6 months (+12% vs. −29%, $P = 0.02$). Logistic regression analysis demonstrated on average that a 10% increase in rCBV at 1 month after convection-enhanced delivery of topotecan was associated with 1.7 times the odds of developing progressive disease at 6 months (95% confidence interval [CI] 1.0–2.9 $P = 0.05$). Receiver operating characteristic analysis for determining progressive disease at 6 months showed a greater area under the curve with rCBV (0.867; 95% CI 0.66–1.00) than with change in enhancing tumor volume (0.767; 95% CI 0.51–1.00).**

■ CONCLUSION: **In this selected population of patients with recurrent malignant glioma treated with convection-enhanced delivery of topotecan, early changes in rCBV at 4 weeks after therapy may help predict progression status at 6 months.**

INTRODUCTION

The dismal prognosis in patients with recurrent malignant glioma has driven interest in the development of a wide array of new therapies, including direct interstitial delivery techniques such as convection-enhanced delivery (CED). CED is a local delivery technique that bypasses the blood–brain barrier by delivering drugs through positive pressure bulk flow into the brain via stereotactically placed catheters. This method is designed to help overcome 2 major obstacles in malignant glioma therapy: 1) via bypassing the restrictive nature of the blood–brain barrier, which limits the efficacy of many promising chemotherapeutics; and 2) by virtue of regional drug delivery, CED may be better suited to address the high rate of local recurrence in malignant glioma compared with conventional intravenous chemotherapy.

Key words
- Convection-enhanced delivery
- Perfusion magnetic resonance imaging
- Topotecan

Abbreviations and Acronyms
CED: Convection-enhanced delivery
DCE: Dynamic contrast-enhanced
DSC: Dynamic susceptibility contrast-enhanced
GBM: Glioblastoma multiforme
MGMT: Methylguanine methyltransferase
MRI: Magnetic resonance imaging
NPD: Nonprogressive disease
PD: Progressive disease
PRM: Parametric response mapping
RANO: Response Assessment in Neuro-Oncology Working Group
ROC: Receiver operator characteristic
RT/TMZ: Radiotherapy and temozolomide chemotherapy

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One of the challenges in developing effective therapy for malignant glioma is the absence of noninvasive imaging biomarkers that can accurately determine antitumor effect early during the course of therapy. Contrast-enhanced magnetic resonance imaging (MRI) is the current key element in clinical assessment of treatment response before and after combined radiotherapy and temozolomide chemotherapy (RT/TMZ) based on the original Macdonald criteria (27) and its recent update by the Response Assessment in Neuro-Oncology Working Group (RANO) (40). Early treatment response may be transient and may not necessarily correlate with a long-term favorable outcome.

This has proven problematic in conventional and experimental treatment response assessment, because early treatment-related imaging changes manifesting as transient increases in contrast enhancement that spontaneously resolve frequently can be indistinguishable from disease progression, commonly referred to as pseudoprogression (5). Patients with pseudoprogression have a spurious increase in contrast-enhancing tumor volume weeks to months after treatment for glioma that improves spontaneously, without any changes in their treatment regimen. There is some speculation as to the responsible mechanisms, although pseudoprogression likely reflects an exaggerated response to effective therapy (9). The accurate prediction of which tumors that exhibit an increase in contrast-enhancing volume early after treatment represent progressive disease (PD) or pseudoprogression has not been established definitively by the use of noninvasive imaging techniques. Definitive diagnosis is dependent upon histology, which must be obtained through invasive procedures. It is of significant clinical interest to identify a noninvasive method of determining which tumors that appeared to be growing early after conventional or experimental therapy were truly progressing and which were exhibiting pseudoprogression and would eventually respond.

Optimal parameters for the noninvasive evaluation of early treatment response to standard or novel therapies such as CED currently are not well defined. Recent advances in multiparametric MRI may provide quantitative information that can aid in monitoring therapeutic response and potentially predict clinical outcome early in the course of therapy. Contrast-enhanced perfusion MRI may offer increased specificity regarding the tumor microenvironment before, during, and after therapy; this information is not readily available or apparent on conventional contrast-enhanced anatomic MRI.

Perfusion MRI-based techniques have demonstrated utility in the grading of gliomas (2, 21-23) and have been shown to be a prognostic marker in predicting survival after therapy (7, 24, 28). Higher-grade tumors tend to have elevated relative cerebral blood volume (rCBV), which highlights the significant role of vascular proliferation in the biology of high-grade gliomas, given the associations between tumor grade, microvessel density, and rCBV (34). Perfusion MRI can play a role in monitoring therapeutic response to either standard (28) or experimental therapies in malignant glioma. For example, changes in the volume transfer coefficient as determined by dynamic contrast-enhanced (DCE) MRI have been shown to correlate with survival even after a single dose of cediranib (33), an experimental vascular endothelial growth factor inhibitor.

The purpose of this study was to examine changes in rCBV and enhancing tumor volume parameters in patients with recurrent malignant glioma treated with CED topotecan. Our hypothesis was that changes in rCBV at 1 month after therapy would correlate with treatment response or failure as determined by 6-month progression status and thus potentially circumvent some of the clinical challenges presented by the pseudoprogression phenomenon. In this work, we used 6-month progression status as the clinical end point of efficacy, which has been endorsed by the North American Brain Tumor Coalition and used in several other studies in the evaluation of therapies for newly diagnosed or recurrent malignant glioma patients (13, 31), in addition to having been shown to be a strong predictor of survival (31).

METHODS

Patient Population

Sixteen patients with recurrent or progressive supratentorial malignant glioma (World Health Organization grade III or IV) who underwent CED of topotecan at Columbia University Medical Center as part of a prospective Phase Ib open-label, nonrandomized trial were selected retrospectively for this Health Insurance Portability and Accountability Act-compliant Institutional Review Board–approved study. All patients in this study previously had therapy with external beam radiation, 15 of 16 patients had surgical resection previously (1 patient had stereotactic biopsy and did not have primary surgical resection because of tumor involvement of the eloquent regions), and a stereotactically accessible enhancing tumor volume on MRI less than 65 cm^3. The 16 patients (11 male, 5 female) had a median age of 50 years (range, 22–71 years); 10 patients had glioblastoma multiforme (GBM), 2 had anaplastic astrocytoma, 2 had anaplastic oligodendroglioma, and 2 had anaplastic ependymoma.

During their course of previous therapy, 12 patients were administered temozolide; 1 patient received bis-chloroethylnitrosourea only; 1 patient received *bis*-chloroethylnitrosourea, thiotepa, and etoposide; 2 patients received imatinib mesylate and hydroxyurea; and 1 patient received 6 courses of bevacizumab and irinotecan. (Please see **Table 1** for demographic details). None of the patients received any treatment in the 4 weeks before receiving topotecan CED. The treatment protocol used in this trial and the patients in this cohort have been previously described in detail in a prospective phase 1b study (6).

At the time of surgery, each patient had tissue biopsy to document tumor recurrence before the placement of CED catheters. In summary, 1 or 2 tunneled infusion catheters (2.5 mm outer diameter, CSF-peritoneal catheter; Integra, Plainsboro, New Jersey, USA) were stereotactically placed directly into tumor or adjacent brain at sites chosen to maximize coverage of the tumor and adjacent infiltrated brain tissue based on a spherical distribution. The externalized catheters were connected to a Medfusion 2010 syringe pump (Medex, Inc; Carlsbad, California, USA). After patients received a 40-mL infusion of topotecan (GlaxoSmithKline; Philadelphia, Philadelphia, USA), catheters were removed at the bedside. Patients returned for clinical follow-up evaluation and a contrast-enhanced MRI every 4 weeks for 16 weeks, then every 8 weeks thereafter, unless there were clinical or radiographic indications for more frequent monitoring.

PD was defined as a greater than 25% increase in enhancing tumor volume at 6 months (confirmed at 7 months) compared