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Post Treatment DSC-MRI is Predictive of Early Treatment Failure in Children with Supratentorial High-Grade Glioma Treated with Erlotinib

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Abstract

Background and Purpose: The role of perfusion imaging in the management of pediatric high grade glioma is unclear. We evaluated the ability of DSC-MRI to determine grade, evaluate post-treatment response and predict treatment failure.

Materials and Methods: Twenty-two patients with high-grade glioma underwent biopsy and were treated with concurrent and sequential radiotherapy and erlotinib as part of a phase I/II clinical trial (NCTXXXX). Pre-, immediate post-radiotherapy, 6-month, and treatment failure DSC MR images were reviewed, registered, and processed for the ratio of CBF and CBV. Processed, derived perfusion, and T1WI, T2WI, and FLAIR MRI sequences were used for segmentation and extraction of tumor perfusion parameters at all time-points. Patient, tumor, treatment, and outcome data were summarized and related to perfusion data.

Results: Regional CBF in tumors increased from diagnosis to post radiotherapy, while they decreased to levels below those at diagnosis from post radiotherapy to 6-month follow up. At 6 months, the median regional CBF was higher in tumors that progressed (median, 1.16) than in those that did not (median, 0.95; $P < .05$). Patients with regional CBF ratios above 1.4 at diagnosis had shorter survival times than did those with regional CBF ratios below 1.4 ($P = .77$). Tumors with a regional CBV above 1.15 at the post-radiotherapy (1- to 3-month) follow-up scan were associated with an earlier time to death than that of tumors with a regional CBV below 1.15 ($P < .05$).

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Ethics Statement: All human and animal studies have been approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Conclusion: Post-treatment perfusion characteristics are prognostic and may help predict survival. Overall, perfusion MRI is useful for managing pediatric high-grade glioma and should be incorporated into future clinical trials.

Keywords

DSC; Perfusion; pediatric; High grade glioma

Introduction:

High-grade glioma (HGG) accounted for 43.8% of CNS deaths in children from 2007-2011 [1]. HGG can generally be classified as grade III anaplastic astrocytoma or grade IV glioblastoma according to the 2016 World Health Organization Classification of CNS Tumors [2]. Despite some advances in identifying effective chemotherapy in adult HGG, optimal chemotherapy and treatment of pediatric HGG has yet to be defined, and long-term survival remains low, with a 5-year survival rate of only 28.4% [3-5].

Assessment of treatment response and treatment failure in HGG can be challenging and is typically evaluated via a combination of clinical examination and conventional MRI. This is especially challenging in pediatric glioma, which uncommonly enhances on post-gadolinium T1WI at diagnosis but may develop enhancement in response to treatment (pseudoprogression and pseudoresponse) without an actual change in tumor size [6, 7]. Furthermore, the role of changes in the FLAIR volume at response and progression are poorly defined [6, 8]. Because of these issues, advanced imaging techniques such as perfusion MRI may be useful in defining response/failure in HGG. Although literature describing the role of perfusion in pediatric glioma is sparse, the results of multiple adult HGG studies suggest a role for perfusion in determining tumor grade, [9-11] prognostication, [12-15] and assessing response to therapy [16-19].

In a phase I/II clinical trial (NCTXX), erlotinib, [20] an epidermal growth factor receptor inhibitor, was given for 2 years during and after conformal radiotherapy following maximum surgical resection in 58 pediatric patients with supratentorial HGG [21]. As part of the trial, DSC-MRIs were collected prospectively in all patients. The purpose of this manuscript is to evaluate the role of regional CBF and regional CBV parameters in describing the natural history of pediatric HGG in patients treated with erlotinib, and more specifically, to evaluate the potential of these parameters in differentiating tumor grade, identifying progression, and predicting early treatment failure.

Methods:

Patient Population

Patients analyzed were part of a phase I/II clinical trial (NCTXXX) testing the use of erlotinib in patients aged 3-21 years with non-metastatic, newly diagnosed HGG. Eligibility criteria for enrollment were reported in a previously published study of the results of the clinical trial [21]. This analysis of imaging exploratory objectives performed as a part of XXX was approved by the institutional review board. There were 58 patients with high-

grade tumors in the trial. Because the goal of this study was to identify perfusion changes in tumor, we analyzed data of patients that underwent biopsy-only procedures (n=22), and excluded patients that received gross or sub-total resection procedures. Biopsy was defined as < 10% of tumor resection. Thirty-six patients were excluded from our study: 35 had gross total or sub-total resection, and 1 had a tumor that was reclassified as a high-grade neuroepithelial tumor.

Trial Treatment

The details of protocol therapy have been previously described [21]. Following biopsy and/or maximum safe surgical resection, patients received 54-59.4 Gy local radiotherapy administered at a dose of 1.8 Gy per fraction, 5 days a week, for 6-6.5 weeks. Treatment volume encompassed the entire tumor as defined by T1WI, T2WI, and FLAIR images, with a 2.5-cm margin to account for microscopic disease and patient positioning or movement during treatment. Erlotinib was initiated on the first day of radiotherapy at 120 mg/m² per day. Patients received 26 courses (28 days/course) of erlotinib for a total 2 years of treatment unless the tumor progressed or intolerable toxicities occurred.

Imaging Acquisition Parameters

Imaging was performed at diagnosis, 4-6 weeks after the completion of therapy (1st post-therapy scan), and every 12 weeks thereafter until completion of therapy. Upon completion of therapy, imaging was to be performed every 3 months up to 24 months and then continued every 6 months, if clinically indicated, until 60 months post treatment. Tumor perfusion examinations were conducted by administering contrast in divided injections of 2 mL per kg administration. Sagittal T1, transverse PD/T2, transverse FLAIR, and transverse 2D FLASH T1 sequences were performed before contrast was administered. One half of the calculated dose of Omniscan (Gadodiamide) (GE Healthcare, Chicago, IL) was then administered. DSC-MRI images were obtained after the first contrast injection by using selected MRI slices that contained the area of interest (i.e., the most biologically viable part of the tumor). After this step, a T2* perfusion examination was performed through the whole brain by using the remaining halfdose of contrast. The imaging parameters used were as follows: TR = 1919 ms; TE = 50 ms; ET = 1; slice thickness = 5 mm; and slice separation = 5 mm. Post-contrast T1 imaging was performed by using 3D sagittal, axial, and coronal 2D FLASH sequences. Iron-calcium sequence, multi-voxel 2D spectroscopy, and DTI sequences were performed last. The perfusion, diffusion, and multi-voxel spectroscopy data were post-processed off-line after the imaging examination.

Image Analysis

Perfusion images were analyzed at 3 or 4 time-points: initial diagnosis (pre-treatment), post radiotherapy (8 weeks), follow up, and progression (if present). Follow-up scans used were at 6 months for comparison to the immediate post-treatment MRI if there was no progressive disease.

ROI Delineation/Segmentation

Image post-processing was performed by using IntelliSpace Portal Version 7.0 (Philips Healthcare, Best, The Netherlands). The middle cerebral artery was manually selected for computation of the arterial input function. The tumor volume was delineated by using T2-weighted, FLAIR, or T1-weighted images. A contralateral ROI was drawn in normal brain tissue for each contour. For midline tumors, an ROI was drawn in the normal brain tissue of one of the hemispheres.

Data Processing

Data were extracted from IntelliSpace to determine the segmented tumor volume and reference normal volume. The average regional CBV and regional CBF values were extracted from each DSC-MRI examination. The regional CBF and regional CBV were evaluated both as absolute quantities and as ratios of the tumor to normal values. Extracted data were managed in Excel 2013.

Statistical Analysis

Continuous data were summarized by using nonparametric descriptors and tested across groups by using the Kruskal-Wallis or Mann-Whitney tests and Chi-square or Fisher's exact tests. Time-to-event data were summarized by using the Kaplan-Meier estimator and tested across strata by using the log-rank test. All statistical analyses were completed in SAS v9 (SAS Institute, Cary, NC).

Results:

Patient Characteristics:

Twenty-two patients met criteria for analysis: 17 had World Health Organization grade III glioma, and 5 had World Health Organization grade IV glioma (Supplementary Table 1). The median age at diagnosis was 9.9 years (range, 4.3-20.6 years). Fifteen patients required steroids at diagnosis (Supplementary Table 1). All patients received 3D conformal radiotherapy to 59.4 Gy in 1.8-Gy daily fractions over 6.5 weeks with concurrent and adjuvant erlotinib.

Outcomes

Disease progression was observed in 91% of patients, and all patients were dead of disease within 5 years (Fig 1, Table 1). Two patients died secondary to non-tumor-related causes (acute pancreatitis and trauma due to a sledding accident). Median time-to-progression was 9.8 months (95% CI, 5-15 months); median overall survival time was 12.0 months (95% CI, 9.7-19.2 months).

Imaging Review

Images from all 22 patients were analyzed at diagnosis. Images from 16 patients were analyzed post radiotherapy (8 weeks). Four patients did not have post-radiotherapy DSC images available, and 2 patients had images that could not be analyzed due to patient motion or inadequate arterial input function. Of the 10 patients whose disease showed progression, 9

were evaluated (Supplementary Figure 1). One patient had a shunt that caused a metallic artifact, rendering the images unusable. Of the 22 patients, 12 either dropped out of the trial or had tumors that did not fail treatment. Follow-up imaging was available for 7 of the 12 without progression.

Perfusion Parameters

The CBF and CBV ratios of tumor to normal tissue were normally distributed among the study group. The median CBF ratio was 1.05 (range, 0.54-1.72), and the median CBV ratio was 1.09 (range, 0.309-7.96) across all time-points.

Perfusion Parameters across Grade

The CBV ratio at diagnosis did not vary significantly between grade III (median = 1.12; range, 0.49-1.6) and grade IV (median = 1.08; range, 0.77-1.52; $P = .59$) tumors (Fig 2). Similarly, the CBF ratios of grade III (median = 1.12; range 0.52-1.7) and grade IV tumors (median = 1.2; range, 0.62-1.4, $P = .81$) were not significantly different.

Change in Perfusion Parameters over Time

The CBF ratio increased from diagnosis (median = 1.05; range, 1.04-1.72) to the post-radiotherapy scan (median = 1.16; range, 0.69-1.60) (difference in means = 0.07, $P < .05$) and decreased from the post-radiotherapy scan to the follow-up (6 month) scan (median = 0.96; range 0.56-1.26, difference in means = 0.2, $P < .05$) in patients who did not experience disease progression (Fig 3) The CBF ratio at 6 months in patients without disease progression was lower than the ratio in patients at diagnosis (difference in means = 0.13, $P < .05$). The CBV ratio stayed relatively constant over time, with no statistically significant differences (median at time points: diagnosis = 1.09, post-radiotherapy = 1.00; 6 months = 1.14).

Differences in Perfusion at Progression and in Stable Disease

The CBF and CBV ratios of patients who experienced tumor progression were compared to those of patients who did not (Fig 4). The CBF ratio for patients with disease progression (median = 1.16; range, 0.7-1.6) was significantly higher than the CBF ratio in patients without disease progression (median = 0.95; range, 0.6-1.3) ($P < .05$). The CBV ratios in patients with disease progression (median = 1.2; range, 1.1-1.3) were not significantly higher than those in patients without progression (median = 0.95; range, 0.64-1.42; $P = .07$).

Predicting Overall Survival from Diagnosis Perfusion Parameters

Patients with tumors having CBF ratios above a receiver operating characteristic-directed cut off of 1.4 at diagnosis did not have a significantly shorter time to death than those with lower CBF ratios (respective 18-month survival of 0% vs. 42%, $P = .077$) (Fig 5A). All patients with CBF ratios above 1.4 at diagnosis died within 1 year of completing radiotherapy.

Predicting Overall Survival from Post-radiotherapy Perfusion Parameters

Patients with tumors with CBV ratios above a receiver operating characteristic-directed cut off of 1.15 at their 8-week MR evaluation had a shorter time to death than those with CBV ratios below 1.15 (respective median survival of 11.2 months 95% CI 7.1-15.3 vs. 19.6 months 95% CI 10.5-58.9, $P = .05$) (Fig 5B). All patients with CBV ratios above 1.15 died within 2 years of completing radiotherapy.

Discussion:

We systematically evaluated the role of regional CBF and regional CBV in patients with pediatric HGG who were treated with concurrent chemoradiotherapy when biopsy alone was not possible. Perfusion imaging parameters were differentially distributed to varying degrees according to tumor grade, progression, and predisposition for early treatment failure.

We noted a consistent rise and fall in perfusion parameters from diagnosis, post-radiotherapy, and to 6-month follow up in patients whose disease did not progress. We found that the CBF ratio increased from diagnosis to post treatment and then decreased from post treatment to 6 months. Conversely, the CBV ratio did not change significantly over the course of treatment. These results are similar to those published in a study of 35 patients with pediatric diffuse intrinsic pontine glioma [22]. CBF and CBV increased and tumor volume decreased during combined radiotherapy and vandetanib (an inhibitor of epidermal and vascular endothelial growth factor receptor) therapy [22]. In that study, these changes diminished in follow-up scans until tumor progression [22]. Taken together with our findings, these results suggest that perfusion parameters in pediatric HGG treated with epidermal growth factor inhibitors increase during therapy and decrease after therapy until progression.

Other researchers suggest that increased tumor blood perfusion after treatment with anti-angiogenic drugs is a result of decreased permeability of the blood vessels in response to treatment [23]. Increases in perfusion could also be caused by irradiation. CBV is reported to increase in HGG after the first week of RT: one explanation is that radiotherapy may cause a reduction in vascular permeability, increasing the perfusion parameters [24]. Either way, a reduction in blood vessel permeability may be the cause for our findings of perfusion changes.

The CBF ratio among patients whose disease progressed was significantly higher than that of those without disease progression, but the CBV ratio was not. Methods of calculating CBV and CBF vary among studies, but our findings coincide with several reports that progressive tumors have higher perfusion parameters than do stable tumors, [13, 15, 19, 25] indicating that perfusion imaging shows efficacy in determining progression in pediatric HGG.

Although we found no statistically significant differences in CBV and CBF ratios of grade III and grade IV tumors at diagnosis, several studies in adult patients noted the potential of CBV to differentiate low-grade (reduced perfusion) from high-grade (high perfusion) gliomas [26, 10, 11]. For example, researchers have differentiated between HGG and low-

grade glioma and between grade III and grade IV tumors in adult glioma by using plasma volume and time-dependent leakage constant measurements from dynamic contrast-enhanced MRI [9]. Regions of increased perfusion on DSC-MRI may be identified before biopsy to ensure appropriate biopsy site selection [27]. Differentiating between grade III and grade IV in pediatric gliomas on the basis of perfusion parameters may require a sample size larger than that of our cohort. Additionally, tumor heterogeneity and sampling error may lead to less accurate histological grading in cases in which complete resection is not possible.

Identifying tumors at high risk for recurrence is critical in the management of localized disease [28]. We found that a CBF ratio cut-off of 1.4 in the diagnosis scans was predictive of shortened time to death. CBV and CBF ratios have been previously demonstrated to predict prognosis after treatment in HGG [29, 16, 12, 17, 13, 18, 14, 30, 19]. Although methods for determining CBF and CBV vary, several studies in adults have reported that patients with a higher CBV and/or CBF after treatment have a faster time to progression and shorter overall survival than do patients with lower values. Tumor aggressiveness and malignancy are associated with neovascularization and increased intra-tumoral perfusion [31, 11, 32, 33]; thus, decreased intra-tumoral perfusion post treatment may represent a quiescent/responding tumor.

Two recent studies of patients with HGG treated with epidermal growth factor receptor inhibitors (such as erlotinib) have different findings than those mentioned above. One group reported that elevated tumor perfusion during and after radiotherapy was correlated with longer progression-free and overall survival in patients with pediatric diffuse intrinsic pontine glioma treated with vandetanib [22]. Another group found similar results in treatment of 30 adult patients with recurrent glioblastoma with cediranib, a vascular endothelial growth factor receptor inhibitor. Increased intra-tumoral perfusion during treatment was associated with longer progression-free and overall survival times than those found in patients whose tumors showed a decreased or stable perfusion map [23]. Others have suggested that increased tumor blood perfusion is a result of decreased permeability of the blood vessels normalized by anti-angiogenic agents [23].

Although our treatment was similar to that used by two of these groups, our results about prediction of overall survival do not correlate with theirs. This may highlight differences in the mechanism of action of concurrent therapies. Vandetanib is only a modest epidermal growth factor receptor inhibitor, and cediranib has minimal to no epidermal growth factor receptor inhibitor activity but substantial anti-vascular endothelial growth factor receptor activity. However, a literature review of 13 studies using bevacizumab, a vascular endothelial growth factor antibody, to treat recurrent glioma found that a decrease in regional CBV after treatment was most often correlated with longer progression-free and overall survival times [29], similar to what was found in our study.

Inherent in any study of a rare disease are the limited numbers of cases with which to test a hypothesis. Our study is further reduced in size by the limited proportion of cases having gross residual tumor at the time of treatment. Cohort attrition was apparent in our series, as patients were lost to on-site imaging follow-up, disease progression, and death. This loss

significantly limited the study sample size. Although contrast injection and scan timing can be roadblocks in generating reproducible results, the perfusion parameters for each case were relatively consistent, with an acceptable number of outliers. Occasional spurious values in perfusion parameters may be further optimized in future studies.

Conclusions:

Compared to adult HGG, pediatric HGG appears to have lower perfusion values at baseline [11]. At the time of progression, the CBF and CBV were higher than at diagnosis, albeit at absolute values lower than those of adults. Additionally, combined modality therapy seems to disrupt the blood brain barrier, thus increasing the CBF values on treatment, only to have them nadir below diagnosis levels. Finally, the resultant post-radiotherapy perfusion characteristics are prognostic and may be beneficial in predicting overall survival. Overall, perfusion MRI shows utility in management of pediatric HGG and should be considered for incorporation into future clinical trials.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviation Key:

HGG high-grade glioma

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FIG 1.
Overall Survival, Progression-free Survival, and Survival from Progression.

FIG 2. CBF (A) and CBV (B) Ratios across Histological Grade.
CBV and CBF ratios were obtained from images at diagnosis.

FIG 3. Change in CBF (A) and CBV (B) Ratios over Time.

CBF and CBV ratios at each of 3 time points are shown. Statistically significant results ($P < .05$) are indicated by brackets and asterisks.

FIG 4. CBF and CBV Ratios at Progression and at 6 Months in Patients without Disease Progression.

The histogram plots on the left (A & C) show that the CBF and CBV ratios in both populations were normally distributed, with the CBF and CBV ratios in patients whose disease progressed (B & D) being shifted to the right relative to those of the patients whose disease did not progress.

FIG 5. Relationship between Post-radiotherapy CBV Ratio and Time to Death.

All patients with a CBV ratio > 1.15 at 1 to 3 months post radiation therapy died within 2 years. Patients with CBV ratios < 1.15 had a longer time to death.

Table 1:**Patient Outcomes**

		N	% or M (95% CI)
Alive at last follow-up?	No	22	100%
	Yes	0	0%
Progression?	No	2	9%
	Yes	20	91%
Steroids at Progression?	No	17	77.3%
	Yes	5	22.7%
Time to Progression (months)		22	9.8 (5-14.9)
Overall Survival (months)		22	12.0 (9.7-19.2)
Overall Survival from Recurrence (months)		20	3.6 (1.7-6.0)

M = Median.