Neuro-Oncology

Neuro-Oncology 17(11), 1538–1540, 2015

Letter to the Editor

Dynamic susceptibility contrast MRI measures of relative cerebral blood volume continue to show promise as an early response marker in the setting of bevacizumab treatment

We read with interest Whitney Pope's recent editorial[1] in *Neuro-Oncology* on the paper by Kickingereder et al[2] addressing the utility of relative cerebral blood volume (rCBV) derived from susceptibility-contrast perfusion-weighted MRI for determining therapeutic response in bevacizumab-treated recurrent glioblastoma multiforme (GBM). Kickingereder and Pope contend that although pretreatment rCBV may be a predictive marker of overall survival (OS), there is no evidence supporting post-bevacizumab change in rCBV from baseline as an early response marker. We caution against premature dismissal of rCBV change as an early predictor of treatment response.

Not discussed in Pope's editorial was a recent publication by Schmainda et al[3] demonstrating, in a multicenter trial organized by the American College of Radiology Imaging Network (ACRIN), that bevacizumab-treated recurrent GBM patients with positive versus negative changes in tumor rCBV from pretreatment baseline had highly significant differences in OS. Although these results appear contradictory to those of Kickingereder as well as another recent paper by Schmainda et al,[4] they are actually consistent and potentially offer new insights regarding treatment response and the optimal timing of imaging. Specifically, rCBV changes measured 2 and 16 weeks, but *not* 8 weeks, after bevacizumab initiation in the ACRIN study predicted OS. Similarly, Kickingereder[2] (Table 2) and Schmainda[4] (Fig. 5b) found that 8-week changes in rCBV were nonpredictive of OS. Therefore, these studies are not inconsistent, and the conclusion that posttherapy rCBV changes are generally nonpredictive of OS appears unfounded. *It may all depend on the time at which posttreatment imaging is performed.* It remains unclear why 2- and 16-week measurements may be more meaningful than 8-week measurements, but the pathophysiology of GBM is complex and dynamic, and the prognostication of rCBV measures may vary at different time points.

We analyzed the pretherapy results from the multicenter ACRIN trial and found that contrary to the single-center data from Kickingereder[2] and Schmainda,[4] baseline rCBV *did not* predict OS-1 (AUC = 0.55–0.62 for all 21 patients with perfusion MRI). However, intersite perfusion MRI methodologies (eg, MRI equipment manufacturer, field strength, spin- or gradient-echo technique, echo time) were more variable than for single-center studies. This result suggests that change in rCBV may be more consistent than absolute rCBV in the multicenter setting. It is quite possible that if consistency between sites is improved, baseline rCBV may someday be shown to predict OS in a multicenter trial; but at present, change from baseline may be a more robust measurement in this setting. That being said, we agree with Pope's contention that lack of standardization hampers the application of perfusion imaging but caution against viewing an arterial input function region of interest for normalization of rCBV as a panacea. Such normalization will vary by hematocrit and selection method,[5] with recent evidence that rCBV repeatability is worse when an arterial input function is used for its computation.[6] Transformation of rCBV to a standardized scale[7] provides a viable alternative and has been successfully used in a multicenter setting.[3]

Kickingereder and Pope also postulated that pretreatment rCBV measures alone are sufficient to predict response to bevacizumab. Schmainda[4] found that although low baseline rCBV predicted longer OS, subsequent change in posttreatment rCBV further substratified patients. Patients with high baseline rCBV may have shorter OS than patients with low rCBV, but may relatively benefit from bevacizumab. The ACRIN 2-week results suggest that rCBV change identifies those patients for whom this is true, providing a *modulation* of the inherent OS predicted by baseline rCBV. In fact, after adjusting for baseline rCBV in the ACRIN data, rCBV change at week 2 still correlates significantly with OS. A recent sub-analysis of the ACRIN perfusion data presented at the 2014 meeting of the Radiology Society of North America demonstrated that patients not progressing on conventional postcontrast T1-weighted imaging could be substratified into relatively short and long OS based on rCBV change from baseline at 2 weeks posttreatment initiation.[8] It is therefore premature to discount the added value of posttreatment change in rCBV, and at the very least a larger multicenter trial exploring both baseline rCBV and 2-week posttreatment change in rCBV is merited and may be practice changing if the additional time point is found to be beneficial.

We are grateful for the opportunity to address important points raised by Kickingereder and Pope regarding rCBV measures for the evaluation of bevacizumab response in recurrent GBM. Our combined multiyear experience with perfusion MRI and recent involvement with the ACRIN clinical trials have further strengthened our belief that rCBV has promise as an important early response marker in the setting of bevacizumab treatment, and we are hopeful that the additional evidence provided herein will encourage support for its continued evaluation.

Funding

This study was supported by NIH/NCI (grant no. R01 CA082500 and U01 176110 to K.M.S).

Conflict of interest statement. Kathleen M. Schmainda has ownership interest in Imaging Biometrics LLC.

Jerrold L. Boxerman, Kathleen M. Schmainda, Zheng Zhang, and Daniel P. Barboriak
Medical College of Wisconsin, Department of Radiology, Milwaukee, Wisconsin

Corresponding Author: Kathleen M. Schmainda, PhD, Medical College of Wisconsin, Department of Radiology, 8701 Watertown Plank Road, Milwaukee, WI 53226 (kathleen@mcw.edu).

References

1. Pope WB. Predictive imaging marker of bevacizumab efficacy: perfusion MRI. *Neuro Oncol*. 2015;17(8):1046–1047.
2. Kickingereder P, Wiestler B, Burth S, et al. Relative cerebral blood volume is a potential predictive imaging biomarker of bevacizumab efficacy in recurrent glioblastoma. *Neuro Oncol*. 2015;17(8):1139–1147.
3. Schmainda KM, Zhang Z, Prah M, et al. Dynamic susceptibility contrast MRI measures of relative cerebral blood volume as a prognostic marker for overall survival in recurrent glioblastoma: results from the ACRIN 6677/RTOG 0625 multicenter trial. *Neuro Oncol*. 2015;17(8):1148–1156.
4. Schmainda KM, Prah M, Connelly J, et al. Dynamic-susceptibility contrast agent MRI measures of relative cerebral blood volume predict response to bevacizumab in recurrent high-grade glioma. *Neuro Oncol*. 2014;16(6):880–888.
5. Boxerman JL, Hamberg LM, Rosen BR, Weisskoff RM. MR contrast due to intravascular magnetic susceptibility perturbations. *Magn Reson Med*. 1995;34(4):555–566.
6. Jafari-Khouzani K, Emblem KE, Kalpathy-Cramer J, et al. Repeatability of cerebral perfusion using dynamic susceptibility contrast MRI in glioblastoma patients. *Transl Oncol*. 2015;8(3):137–146.
7. Bedekar D, Jensen T, Schmainda KM. Standardization of relative cerebral blood volume (rCBV) image maps for ease of both inter- and intrapatient comparisons. *Magn Reson Med*. 2010;64(3):907–913.
8. Boxerman JL, Zhang Z, Schmainda KM, et al. Early post-bevacizumab change in rCBV from DSC-MRI predicts overall survival in recurrent glioblastoma whereas 2D-T1 response status does not: results from the ACRIN 6677/RTOG 0625 multi-center study. RSNA 100th Scientific Assembly. Chicago, IL, 2014.

Received 20 July 2015; accepted 22 July 2015
Advance Access date 11 September 2015

doi: 10.1093/neuonc/nov163

Reply to Letter

Evidence for rCBV as an early response marker following bevacizumab treatment

I appreciate the thoughtful letter from Schmainda et al. regarding the utility of rCBV derived from MRI as a biomarker of response to bevacizumab therapy in patients with recurrent glioblastoma (GBM). The authors cite their recent work in which they found that tumoral rCBV changes were predictive of overall survival at 2 and 16 weeks, but not 8 weeks, after the start of bevacizumab therapy in patients with GBM.[1] Certainly this issue is not settled science, and I hope that further studies will be performed by the authors or others to clarify the timing at which perfusion imaging adds value to standard MRI in the assessment of patients with brain tumors. In my editorial,[2] I suggest that the use of rCBV as an early response marker for bevacizumab therapy is not well supported to date. On one hand, there are the data from the authors, based on a cohort of 13 patients (point of reference: n for the Kickingereder et al[3] paper showing a relationship between pretreatment rCBV and outcomes was 71) suggesting a relationship between changes in rCBV and survival at 2 and 16 weeks. Interestingly, no relationship was found at 8 weeks, when the cohort size was 17 rather than 13. (In the interests of full disclosure, I was the associate editor who recommended that the authors' paper be published.) On the other hand, because negative results are typically (and unfortunately) unreported, we do not know how many patients with perfusion data treated with bevacizumab were similarly analyzed over the last decade but whose data were never published because of the lack of association between rCBV changes and outcomes. Based on conversations with colleagues over the years, I would suggest this is not a few, so I think it is important to consider publication bias for positive results. This was part of the rationale for suggesting that Schmainda et al's[1] recent study of 13 patients notwithstanding, the evidence in support of rCBV as an early response marker to bevacizumab therapy is not as robust today as would have been predicted 10 years ago.

Whitney B. Pope
University of California, Los Angeles, California

Corresponding Author: Whitney B. Pope, MD, PhD, UCLA, Radiology, 757 Westwood Plaza, 1621E, Los Angeles, CA 90095 (wpope@mednet.ucla.edu).

References

1. Schmainda KM, Zhang Z, Prah M, et al. Dynamic susceptibility contrast MRI measures of relative cerebral blood volume as a prognostic marker for overall survival in recurrent glioblastoma: