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CLINICAL STUDY

Apparent diffusion coefficient histogram analysis stratifies progression-free and overall survival in patients with recurrent GBM treated with bevacizumab: a multi-center study

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Abstract We have tested the predictive value of apparent diffusion coefficient (ADC) histogram analysis in stratifying progression-free survival (PFS) and overall survival (OS) in bevacizumab-treated patients with recurrent glioblastoma multiforme (GBM) from the multi-center BRAIN study. Available MRI's from patients enrolled in the BRAIN study ($n = 97$) were examined by generating ADC histograms from areas of enhancing tumor on T1 weighted post-contrast images fitted to a two normal distribution mixture curve. ADC classifiers including the mean ADC from the lower curve (ADC-L) and the mean lower curve proportion (LCP) were tested for their ability to stratify PFS and OS by using Cox proportional hazard ratios and the Kaplan–Meier method with log-rank test. Mean ADC-L was 1,209 $\times$ 10^{-6}mm^2/s $\pm$ 224 (SD), and mean LCP was 0.71 $\pm$ 0.23 (SD). Low ADC-L was associated with worse outcome. The hazard ratios for 6-month PFS, overall PFS, and OS in patients with less versus greater than mean ADC-L were 3.1 (95 % confidence interval: 1.6, 6.1; $P = 0.001$), 2.3 (95 % CI: 1.3, 4.0; $P = 0.002$), and 2.4

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(95 % CI: 1.4, 4.2; $P = 0.002$), respectively. In patients with ADC-L <1,209 and LCP >0.71 versus ADC-L >1,209 and LCP <0.71, there was a 2.28-fold reduction in the median time to progression, and a 1.42-fold decrease in the median OS. The predictive value of ADC histogram analysis, in which low ADC-L was associated with poor outcome, was confirmed in bevacizumab-treated patients with recurrent GBM in a post hoc analysis from the multicenter (BRAIN) study.

Keywords Apparent diffusion coefficient · Glioblastoma multiforme · Progression-free survival

Introduction

Glioblastoma (GBM), the most aggressive and lethal primary brain tumor, respond unpredictably to standard therapy, resulting in highly variable patient survival [1]. Because of this variable response, a biomarker to predict treatment susceptibility could help guide patient care and avoid side effects from ineffective therapies. In clinical practice, the reference standards of patient response to therapy are 6-month progression-free and overall survival (PFS and OS) [2]. The MacDonald criteria, based on measurable changes in contrast-enhancing lesions[3], and the recently proposed response assessment in neuro-oncology (RANO) criteria that also takes into account non-enhancing tumor, have been the primary paradigms for assessing response in recent years [4]. However, tumor burden may be difficult to accurately quantify, especially in patients undergoing anti-angiogenic therapy [5]. Recently, the FDA approved the anti-angiogenic drug bevacizumab (a humanized monoclonal antibody to vascular endothelial growth factor, VEGF) for use in patients with recurrent GBM. Currently, there are no prospectively validated predictive or prognostic biomarkers for bevacizumab response. Biomarkers that either predict clinical outcome following a specific treatment such as bevacizumab, or those that are early markers of tumor response after treatment initiation, are of major interest, as well as a challenge, in clinical oncology research [6].

The apparent diffusion coefficient (ADC), derived from diffusion-weighted imaging (DWI), is a physiologic parameter calculated based on characteristics of water diffusion within the tissue of interest [7]. In neoplasms, lower ADC values have been shown to correlate with higher cell density [8]. Conversely, higher ADC values have been observed in regions of necrosis and edema [9]. ADC has been investigated as a biomarker for glioma response in the setting of anti-angiogenic therapy [10–12]. In our previous study [10], we developed a strategy in which whole ADC histograms extracted from enhancing tumor volumes on pre-bevacizumab treatment MR images were fitted with two normal distribution mixture curves. The subsequently generated ADC classifiers, mean ADC from the lower curve (ADC-L), and the mean lower curve proportion (LCP) were shown to accurately stratify 6-month PFS in bevacizumab-treated patients with recurrent GBM. However, the study was conducted in a relatively small patient cohort ($n = 41$) in a single medical center (UCLA). In the current study, we analyzed patient data from the BRAIN trial [13], one of the largest multicenter studies of recurrent GBM patients treated with bevacizumab, to verify the observed predictive feature of ADC histogram analysis in stratifying the outcomes of bevacizumab-treated patients with recurrent GBM.

Methods

Patients

All patients in the current study were part of the BRAIN trial, which was performed to assess the effectiveness of bevacizumab or bevacizumab and CPT-11 (Irinotecan) in patients with recurrent GBM [13]. For this trial, 167 patients from multiple participating centers who had histologically confirmed GBM at first or second relapse were enrolled. Disease progression that led to enrollment in the study was identified on magnetic resonance imaging (MRI) $\leq$14 days before the baseline treatment. These patients had failed the initial standard care plan including concurrent radiotherapy (RT) and temozolomide (TMZ), and were required to be at least 8 weeks from the completion of radiation therapy. The baseline was defined as the first day when bevacizumab or bevacizumab + CPT-11 treatment

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