Bevacizumab for recurrent glioblastoma case series

2018

The aim of a study of Beppu et al., was to clarify whether arterial spin labeling (ASL) perfusion imaging can assess biological effects from bevacizumab (BEV) therapy as reliably as PET with C-methyl-L-methionine (C-met-PET).

Twenty-four patients with recurrent glioblastoma were examined using both ASL and C-met-PET before and 4 and 8 weeks after starting BEV treatment. Tumor-to-normal brain (T/N) ratios, fluctuations in T/N ratio, and tumor volumes were compared between ASL and C-met-PET. Accuracy of predicting patient with long progression-free survival (PFS) was assessed for T/N ratios and fluctuations for ASL and C-met-PET in each phase and in each period using receiver operating characteristic curves. Between 2 groups of patients assigned by cutoff values from receiver operating characteristic curves, PFS was compared in each phase or in each period.

T/N ratios, fluctuations in ratio, and tumor volumes correlated significantly between ASL and C-met-PET at all time points and all periods. Arterial spin labeling was eligible as a predictor for long PFS only in assessment of fluctuations in T/N ratio. However, the most accurate predictors for long PFS were T/N ratio from C-met-PET at 8 weeks and the fluctuation from baseline to 4 weeks in T/N ratio from C-met-PET.

Blood flows on ASL correlated with accumulations of C-met on PET in recurrent glioblastoma under BEV treatment. Although C-met-PET offered superior accuracy for predicting patients with long PFS from time points, ASL offered reliable prediction of long PFS, provided that fluctuations in T/N ratio between consecutive scans are assessed [1)].

Choi et al. retrospectively reviewed patients with recurrent GBM who received bevacizumab to identify biomarkers for predicting clinical response to bevacizumab. Following defined criteria, the patients were categorized into two clinical response groups, and their genetic and transcriptomic results were compared. Angiogenesis-related gene sets were upregulated in both responders and nonresponders, whereas genes for each corresponding angiogenesis pathway were distinct from one another. Two gene sets were made, namely, the nonresponder angiogenesis gene set (NAG) and responder angiogenesis gene set (RAG), and then implemented in independent GBM cohort to validate our dataset. A similar association between the corresponding gene set and survival was observed. In NAG, COL4A2 was associated with a poor clinical outcome in bevacizumab-treated patients. This study demonstrates that angiogenesis-associated gene sets are composed of distinct subsets with diverse biological roles and they represent different clinical responses to anti-angiogenic therapy. Enrichment of a distinct angiogenesis pathway may serve as a biomarker to predict patients who will derive a clinical benefit from bevacizumab [2)].

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Patients with Karnofsky performance status ≥60, history of standard fractionated initial radiation, tumor volume at recurrence ≤40 cm3, and absence of brainstem or corpus callosum involvement were eligible. A standard 3+3 phase 1 dose escalation trial design was utilized, with dose-limiting toxicities defined as any grade 3 to 5 toxicities possibly, probably, or definitely related to radiation. Bevacizumab was given at a dose of 10 mg/kg every 2 weeks. Hypofractionated stereotactic reirradiation was initiated after 2 bevacizumab doses, delivered in 3 fractions every other day, starting at 9 Gy per fraction.

A total of 3 patients were enrolled at the 9 Gy × 3 dose level cohort, 5 in the 10 Gy × 3 cohort, and 7 in the 11 Gy × 3 cohort. One dose-limiting toxicity of grade 3 fatigue and cognitive deterioration possibly related to hypofractionated stereotactic reirradiation was observed in the 11 Gy × 3 cohort, and this dose was declared the maximum tolerated dose in combination with bevacizumab. Although no symptomatic radionecrosis was observed, substantial treatment-related effects and necrosis were observed in resected specimens. The intent-to-treat median overall survival was 13 months.

Reirradiation using a 3-fraction schedule with bevacizumab support is feasible and reasonably well tolerated. Dose-escalation was possible up to 11 Gy × 3, which achieves a near doubling in the delivered biological equivalent dose to normal brain, in comparison with our previous 6 Gy × 5 schedule. Promising overall survival warrants further investigation [3].

One hundred sixty-seven patients were randomly assigned to receive bevacizumab 10 mg/kg alone or in combination with irinotecan 340 mg/m(2) or 125 mg/m(2) (with or without concomitant enzyme-inducing antiepileptic drugs, respectively) once every 2 weeks. Primary end points were 6-month progression-free survival and objective response rate, as determined by independent radiology review. Secondary end points included safety and overall survival.

RESULTS: In the bevacizumab-alone and the bevacizumab-plus-irinotecan groups, estimated 6-month progression-free survival rates were 42.6% and 50.3%, respectively; objective response rates were 28.2% and 37.8%, respectively; and median overall survival times were 9.2 months and 8.7 months, respectively. There was a trend for patients who were taking corticosteroids at baseline to take stable or decreasing doses over time. Of the patients treated with bevacizumab alone or bevacizumab plus irinotecan, 46.4% and 65.8%, respectively, experienced grade > or = 3 adverse events, the most common of which were hypertension (8.3%) and convulsion (6.0%) in the bevacizumab-alone group and convulsion (13.9%), neutropenia (8.9%), and fatigue (8.9%) in the bevacizumab-plus-irinotecan group. Intracranial hemorrhage was noted in two patients (2.4%) in the bevacizumab-alone group (grade 1) and in three patients (3.8%) patients in the bevacizumab-plus-irinotecan group (grades 1, 2, and 4, respectively).

Bevacizumab, alone or in combination with irinotecan, was well tolerated and active in recurrent glioblastoma [4].

1)
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