Bevacizumab for recurrent glioblastoma

Bevacizumab (Avastin®) – a monoclonal antibody against VEGF. FDA approved in May 2009 for progressive glioblastoma following prior treatment based on two trials: the BRAIN study, AVF3708g 1) and NCI 06-C-0064E 2).

Given as 10 mg/kg every 2 weeks until disease progression. The reported 6-month PFS rate was 36.0%. The median response durations were 3.9 months and 4.2 months from the two trials. The median OS was 9.3 months 3).

Side effects: gastrointestinal perforations, wound healing complications, hemorrhage, fistula formation, arterial thromboembolic events, hypertension.

Faltings et al. first reported the effect of rechallenging a patient with super-selective intra-arterial cerebral infusion (SIACI) of bevacizumab following disease progression after initial bevacizumab treatment and subsequent alternate clinical trial failure. There is a need to conduct further clinical trials to evaluate the benefits of rechallenge with SIACI versus IV bevacizumab for GBM, further exploring theories of bevacizumab resistance 4).

Some phase 2 trials had reported encouraging progression free survival with Bevacizumab in monotherapy or combined with chemotherapy in glioblastoma. However, phase 3 trials showed a significant improvement in progression free survival without a benefit in overall survival. To date, there are no predictive biomarker of response for Bevacizumab in glioblastoma 5).

There was interest in the role of bevacizumab, alone or in combination with cytotoxic drugs, but the results were conflicting 6) 7) 8) 9).

Given the highly vascular nature of GBM and its high expression of vascular endothelial growth factor and other angiogenic factors, recent investigation has turned to bevacizumab, an antivascular endothelial growth factor monoclonal antibody, for treatment of recurrent GBM. Phase 2 studies demonstrated the efficacy and safety of bevacizumab therapy for recurrent GBM, which led to its approval by the US Food and Drug Administration in 2009 for use in recurrent GBM. Since then, several new Phase 2 studies and retrospective series have demonstrated that bevacizumab significantly increased six-month progression-free survival in patients with recurrent GBM and may do so in new-onset GBM 10).
Further studies in recurrent disease are being conducted; preliminary results of a randomized trial showed favorable results with the combination with CCNU, and final results are awaited. Meanwhile, outside the realm of clinical trials, the current trend appears to be to reserve bevacizumab for use in recurrent disease, or for patients with moderate or severe neurologic symptoms, either in the newly diagnosed or recurrent setting. Further research efforts are needed to determine optimal candidates for this treatment from a molecular standpoint, as well as to develop imaging tools capable of accurately identifying response and progression, and to establish new drug combinations that could result in unquestionable clinical benefit and improved survival in these patients.

**Monitoring response**

In this setting, traditional anatomic MRI methods such as post-contrast T1-weighted and T2-weighted imaging are proving unreliable for monitoring response.

Standardized relative cerebral blood volume (rCBV) derived from dynamic susceptibility contrast MRI is predictive of overall survival (OS) and progression free survival (PFS) in patients with recurrent high-grade brain tumor treated with bevacizumab.

**Overall survival**

Trials on recurrent glioblastoma have shown that bevacizumab alone is able to increase response rate on MRI, median and 6-month progression-free survival (PFS), and modestly overall survival, allowing an improvement of neurological function and a reduction of steroids.

Any drug combination was not superior over bevacizumab alone. A synergistic effect of CCNU has been suggested when added to bevacizumab (BELOB trial), but excluded when added to cediranib (REGAL trial). Phase III trials on bevacizumab in newly diagnosed glioblastoma have shown an improvement of PFS of 3-4 months, but failed to prolong overall survival.

In a randomized trial of bevacizumab for newly diagnosed glioblastoma, the first-line use of bevacizumab did not improve overall survival. Progression-free survival was prolonged but did not reach the prespecified improvement target. (Funded by the National Cancer Institute; ClinicalTrials.gov number, NCT00884741.)

Unexplained is the observation that females had longer overall survival (OS) with BEV than males in patients with progressive glioblastoma.

**Case series**

see Bevacizumab for recurrent glioblastoma case series.

**Case reports**

Bevacizumab for recurrent glioblastoma case reports.

**References**

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