Thompson et al. are to be commended for their review regarding paradoxical effects of bevacizumab (BEV) for the treatment of glioblastoma (GBM). Several comments merit discussion.

The only evidence regarding a decrease in delivery of chemotherapeutics in combination with BEV—a result of BEV-induced tumor vascular normalization and re-establishment of blood brain barrier disruption—is a single, unconfirmed experimental model utilizing vandetanib and temozolomide. The chemosynergy seen when BEV is combined with other solid organ specific chemotherapy regimens resulting in improved survival and approval of BEV for several solid tumors is not mentioned. As chemosynergy has not been documented with BEV and the treatment of GBM, this may partially reflect decreased drug delivery of the combinatorial agent.

Considering the radiographic patterns of recurrence in patients treated with BEV, it has been shown that BEV does not increase invasion. The longer survival of patients treated with BEV results in more apparent invasion due to control of the angiogenic-dependent contrast enhancing primary tumor, the primary target of angiogenic inhibition. Tumor invasion is believed to be an angiogenic independent process that does not respond to BEV and consequently accrues over time.

Pseudoprogression, a treatment effect seen most commonly but not exclusively with chemoradiation, occurs primarily in patients with MGMT promoter methylation, a GBM subgroup (30%) with improved survival. In a subset of patients with pseudoprogression, clinical symptoms emerge that require treatment, not unlike radiation necrosis. Whether BEV has a role in treating this population is uncertain based on the only published trial of up-front BEV in newly diagnosed GBM in which pseudoprogression was rarely seen (due to the decreased permeability effect of BEV), MGMT methylated patients maintained a survival advantage compared to the non-methylated cohort.

In addition, up-front BEV in conjunction with TMZ did not appear to diminish overall survival when compared to patients treated with standard TMZ regimen, which suggests that BEV does not diminish TMZ activity and survival advantage in GBM. What remains challenging regarding the use of BEV in GBM is timing of administration (up-front vs. at recurrence), determining an active partner, validating a survival advantage, identifying biomarkers of response, and determining an effective therapy following disease progression on BEV.

BEV represents an improvement in the treatment of GBM yet better therapy of this cancer remains an unmet need in neuro-oncology.

References

Disclosure: Dr. Chamberlain serves the advisory board and the speakers’ bureau.
We thank Dr. Chamberlain for his comments regarding our article. The first issue concerns drug delivery. Studies are not available showing that bevacizumab directly decreases or increases drug delivery in the CNS.

Careful quantitative drug delivery studies must be performed in animal models and humans to show that gadolinium based contrast agent permeability seen on MRI actually corresponds to delivery of other low molecular weight agents such as temozolomide. As we indicated, bevacizumab and carboplatin appeared to have a synergistic effect in a rat model of glioma. [6] However, rats died with larger tumors suggesting that at least part of the survival increase was due to decreased edema. Similarly, the recent study by Lai et al. in patients that received up-front bevacizumab for GBM demonstrated an increase in progression free survival (PFS) without an increase in overall survival (OS) [5] that may be due to decreased edema.

The second issue is tumor invasion. Dr. Chamberlain suggests that four articles provide evidence that bevacizumab does not increase invasion. In our view, that conclusion is not clear. Other authors have shown that bevacizumab increases invasion [7] and tumor invasion can occur via angiogenic proteins. [8] The issue is not invasion but primarily permeability, concomitant chemotherapy delivery, and inflammation.

The final issue is pseudoprogression, an intense inflammatory response that may be beneficial to patients. Pseudoprogression was rarely seen after up-front bevacizumab in GBM. [5] We suggest this was due to the decreased permeability effect of bevacizumab. Dr. Chamberlain suggests that this decreased incidence of pseudoprogression did not appear to diminish OS, which he primarily attributes to the impact of MGMT promoter methylation in patients. That is an interesting hypothesis but in our view, inflammatory response is vital to the synergism between radiation therapy and temozolomide chemotherapy. In the study by Lai et al., up-front bevacizumab did decrease OS (albeit, not significantly) from 23.1 months to 19.6 months. [5] This effect was particularly apparent in patients under 50 years old and with lower recursive partitioning analysis (RPA) class, [5] groups who typically have the best outcomes in GBM trials.

We agree with Dr. Chamberlain that bevacizumab represents an improvement in the treatment of GBM, but argue that this is only true in progressive disease. Until a survival advantage is demonstrated in treating GBM up front with bevacizumab, there is no clear role for its use in this setting.

References

Disclosures: See original article for full disclosure list.