How Helpful Is Bevacizumab in Recurrent Glioblastoma?

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SYNOPSIS: In a randomized Phase III trial, the addition of bevacizumab to lomustine did not improve overall survival in patients with recurrent glioblastoma compared to lomustine alone.


Glioblastoma (GBM) continues to be one of the deadliest forms of cancer, and although generally rare, it is one of the most common primary brain tumors. Standard treatment includes maximal safe surgical resection followed by concurrent radiation therapy with temozolomide chemotherapy, as well as subsequent adjuvant chemotherapy. Unfortunately, these tumors invariably progress after chemoradiation, and although significant advances have been made (especially with molecular diagnostics and tumor genetic profiling), treatments for recurrent disease are few with only limited efficacy. Bevacizumab, a monoclonal antibody that targets vascular endothelial growth factor (VEGF), is FDA-approved for recurrent GBM. Lomustine, an alkylating nitrosourea with good blood-brain barrier penetration, is an older oral chemotherapy with a similar mechanism of action to temozolomide. The BELOB trial was a multicenter, Phase II study that evaluated the efficacy of single-agent bevacizumab or lomustine vs. the combination of both drugs in progressive GBM. The authors of this study noted potential improved survival with the combination treatment compared to either drug alone, setting the stage for a subsequent Phase III trial that was reported recently in The New England Journal of Medicine.

In this randomized, Phase III trial supported by the European Organisation for Research and Treatment of Cancer, Wick et al randomly assigned patients with initially recurrent GBM after chemoradiation in a 2:1 ratio to receive combination lomustine/bevacizumab or lomustine alone. The trial’s primary endpoint was overall survival, but other indicators, including MGMT promoter methylation status, quality of life, and neurocognitive function, also were assessed.

A total of 288 patients were randomized into the combination group, while 149 patients received lomustine monotherapy. Patients on both drugs received a median of three 6-week cycles, while a median of one cycle of lomustine was given in the monotherapy arm. Although progression-free survival was 2.7 months longer in the combination group, median overall survival was not significantly different (9.1 months with combination bevacizumab/lomustine vs. 8.6 months with lomustine alone). Severe adverse events were more common with the combination treatment (63.6% vs. 38.1% with monotherapy).
Importantly, the addition of bevacizumab did not seem to improve health-related quality of life or neurocognitive function. As expected, patients whose tumors had MGMT promoter methylation (a positive prognostic indicator in GBM that is associated with better response to temozolomide chemotherapy) had better progression-free and overall survival compared to those with unmethylated MGMT promoters (13.5 vs. 8.0 months). However, like the general study population, adding bevacizumab to lomustine did not increase overall survival in the MGMT-methylated group.

COMMENTARY

This international study is impressive in its size and scope, but unfortunately did not demonstrate any improved overall survival with the addition of bevacizumab to lomustine. The results are consistent with the general presumption that although bevacizumab may delay progression, it does not appear to significantly improve overall survival. This is a difficult point for the neuro-oncology community, as bevacizumab remains one of the few FDA-approved therapies for recurrent GBM (data from large studies including AVAglio and RTOG 0825 do not support the use of bevacizumab up-front in newly diagnosed tumors). As an anti-angiogenic agent, bevacizumab contributes to decreased enhancing disease and edema, potentially allowing for tapering of steroids and avoidance of significant steroid-related side effects. However, the addition of bevacizumab did not lead to reduced use of glucocorticoids or improve health-related quality of life in the present study. Further, there was a higher rate of more serious adverse effects with combination treatment, although this could be related to a longer duration of treatment in this group (patients in the lomustine monotherapy arm only received a median of one treatment cycle).

If clinical trials are not available, lomustine monotherapy may be a good option for recurrent disease, especially in tumors with MGMT promoter methylation, which theoretically are more likely to respond to alkylating agents. There does not appear to be any disadvantage in withholding bevacizumab on initial recurrence, especially if there is no significant tumor-related edema.

As with many GBM clinical trials, the negative results of this study highlight the lack of effective options for this deadly disease. There have been great advancements in the molecular characterization of gliomas, but this has not yet translated into improved treatment outcomes (except in cases of IDH1 mutation and 1p/19q codeletion). The greater oncology community has demonstrated fantastic results with immunotherapy (such as checkpoint inhibitors) — sadly, preliminary data indicate only limited efficacy in GBM, which may be related to its lower somatic mutational load and immunosuppressive tumor microenvironment. The success of future treatments may hinge on developing novel preclinical models that are more representative of in vivo human tumors. For patients with this horrible disease, these innovations cannot come soon enough.