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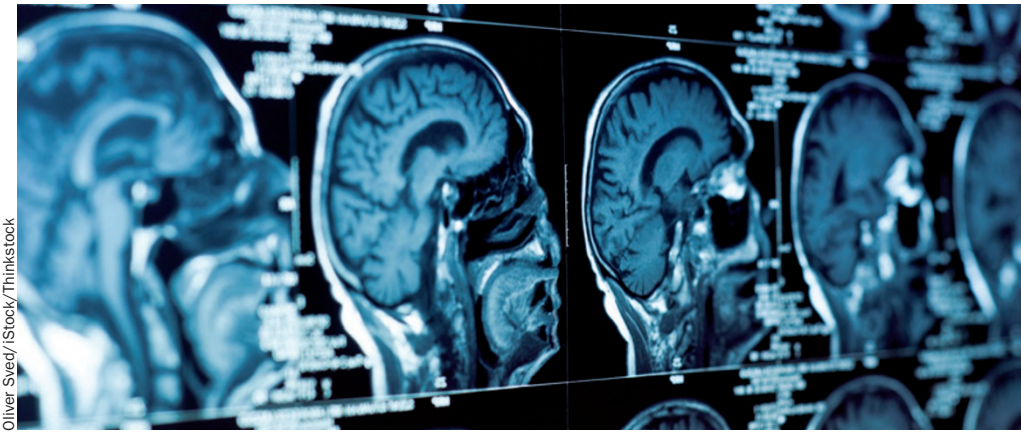
NEURO-ONCOLOGY

Bevacizumab prolongs progression-free survival but not overall survival in newly diagnosed glioblastoma



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Addition of the angiogenesis inhibitor bevacizumab to standard radiotherapy–temozolomide treatment does not improve overall survival in newly diagnosed glioblastoma, according to two randomized, double-blind, placebo-controlled phase III trials published recently in *The New England Journal of Medicine*. Adjuvant bevacizumab was found to increase progression-free survival by about 4 months in both studies, but the findings regarding cognitive functioning and quality of life during the progression-free period were contradictory.

Glioblastoma is associated with intense angiogenesis, which is thought to result from pronounced overexpression of vascular endothelial growth factor A (VEGF-A). Bevacizumab—a humanized monoclonal antibody against VEGF-A—has previously been shown to suppress glioblastoma growth in preclinical models. In recurrent glioblastoma, bevacizumab can improve symptoms and reduce the size of the tumour, but the current studies are the first to assess its usefulness in newly diagnosed glioblastoma.

In both trials, the investigators randomly assigned patients to receive either bevacizumab or placebo in addition to the standard radiotherapy–temozolomide treatment. Overall survival and progression-free survival were the co-primary end points in both studies; in addition, health-related quality of life and cognitive function were assessed.

According to the results of the multinational AVAGlio trial, led by Olivier Chinot from Aix-Marseille University, Assistance Publique–Hôpitaux de Marseille, France, adding bevacizumab to standard therapy did not improve overall survival, but it increased progression-free survival by 4.4 months. Quality of life and Karnofsky performance scores were preserved for longer in patients receiving bevacizumab than in patients receiving placebo. Furthermore, glucocorticoid requirement was reduced in the bevacizumab group, possibly indicating suppressed tumour growth.

In contrast with the study by Chinot *et al.*, the results from the RTOG 0825 trial, led by Mark Gilbert from the University of Texas M. D. Anderson Cancer Center, USA, demonstrated that despite prolonging progression-free survival by 3.4 months, bevacizumab was associated with worse quality of life, decreased neurocognitive function and increased symptom burden. The differences between the trials might arise from variations in statistical methods and assessment time points.

Importantly, the results mean that clinicians should be cautious when administering bevacizumab as first-line therapy for glioblastoma, because the efficacy of the drug is limited, and the patients receiving bevacizumab had higher rate of adverse events than did the patients receiving placebo. Bevacizumab has previously been linked to increased rates of hypertension, intestinal perforation, thrombombolic events and neutropenia, although the adverse effects in the current trials were mostly manageable.

Despite the controversial and perhaps somewhat disappointing results of the AVAGlio and RTOG 0825 trials, bevacizumab remains the most promising systemic treatment for recurring glioblastoma, for which the treatment options are limited. Elucidation of the factors that contribute to bevacizumab-associated suppression of tumour growth, combined with development of imaging or biomarker signatures that would enable patient stratification and individualized treatment, could be beneficial for patients with either newly diagnosed or recurrent glioblastoma.

"One of the most important issues is to identify the patients who will benefit from bevacizumab," Chinot comments. Gilbert agrees on the importance of this goal. "We are in the process of performing advanced molecular testing of the tumour samples collected in the RTOG 0825 trial to determine whether a specific profile can be created," he says. In future, molecular signatures could aid the decision as to which patients should receive bevacizumab as first-line treatment.

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Original articles Gilbert, M. R. *et al.* A randomized trial of bevacizumab for newly diagnosed glioblastoma. *N. Engl. J. Med.* **370**, 699–708 (2014) | Chinot, O. L. *et al.* Bevacizumab plus radiotherapy–temozolomide for newly diagnosed glioblastoma. *N. Engl. J. Med.* **370**, 709–722 (2014)