What have we learned from trials on antiangiogenic agents in glioblastoma?

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. The AVAglio trial has reported an improvement of quality of life, while the RTOG 0825 did not, and suggested a negative impact on neurocognitive functions. The GLARIUS trial, focusing on newly diagnosed glioblastoma without MGMT methylation, suggested an advantage for bevacizumab plus irinotecan. The Phase III CENTRIC trial has excluded any role for cilengitide in addition to standard treatment in newly diagnosed glioblastoma.

The standard management of newly diagnosed glioblastoma multiforme (GBM; Grade IV WHO) involves maximal safe surgical resection, followed by radiotherapy with concomitant and adjuvant temozolomide and treatment options at relapse are limited [1].

GBM has the highest degree of vascular proliferation among solid tumors, and angiogenesis is a crucial step in the development and progression. VEGF is a key growth factor in promoting angiogenesis in gliomas: endothelial cells express and upregulate VEGF and its receptors, resulting in both paracrine and autocrine loops that drive endothelial cells permeability, proliferation and invasion.

The main mechanism of action of anti-VEGF agents, such as bevacizumab (monoclonal antibody against VEGF) or cediranib (oral pan VEGF inhibitor), consists in a transient normalization of the abnormal tumor vasculature, leading to a reduction of the vasogenic edema [3]. The normalization of tumor vessels may theoretically improve the efficacy of chemotherapy by increasing the exposure of tumor cells to cytotoxic drugs and the efficacy of radiotherapy by reducing tumor hypoxia. However, this vascular normalization is time-limited, as the restoration of blood–brain barrier integrity could lead to ischemia and hypoxia thereafter.

In a multi-institutional randomized noncomparative Phase II trial for recurrent GBM (BRAIN Study), 167 patients were assigned either bevacizumab or bevacizumab combined with irinotecan [3]. For those patients on bevacizumab alone, 6-month progression-free survival (PFS) was 43%, objective response rate 28% and median overall survival (OS) 9 months. For those patients on bevacizumab and irinotecan, 6-month PFS was 50%, objective response rate 38% and median OS 8.7 months. Overall, when comparing the results of available Phase II trials on bevacizumab, alone or in combination with irinotecan, with those of standard cytotoxic chemotherapy (i.e., temozolomide, nitrosoureas) in the setting of recurrence, several findings are clear: bevacizumab alone has activity and clearly increases response rate on MRI, PFS at 6 months and median PFS; conversely, the impact of bevacizumab on OS is less clear. The improved

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An open issue is whether any subgroup of patients could benefit most from bevacizumab. This did not emerge from a subgroup analysis of AVAglio trial; on the other hand, a retrospective review on recurrent GBM reported that patients aged ≥55 years had an improved PFS when treated with bevacizumab, and this was related to a higher VEGF expression in tumor specimens [9]. A randomized Phase II trial (ARTE Trial) is being conducted in Switzerland on newly diagnosed GBM patients aged >65 years.

Interestingly, a randomized Phase II trial restricted to newly diagnosed GBM patients without MGMT promoter methylation (Glarius trial) has shown a significant increase in both PFS and OS when adding bevacizumab plus irinotecan to standard radiotherapy and temozolomide [10].

GBMs invariably relapse after initial response to anti-VEGF therapy.

There are different mechanisms by which gliomas can escape antiangiogenic therapy: increased invasion and migration capacities; activation and/or upregulation of alternative proangiogenic signaling pathways; exacerbation of underlying hypoxia; increased pericyte coverage; increase of macrophages; and myeloid cell infiltration. A question that arose after initial bevacizumab trials was whether this drug could significantly increase the risk of diffuse nonenhancing tumor progression (so-called ‘secondary gliomatosis’). Recent retrospective studies and the AVAglio trial have not confirmed this hypothesis.

Another promising avenue of antiangiogenic therapy has been targeting integrins αVβ3 and αVβ5 that are expressed on GBM cells and tumor vasculature. Some activity of a specific inhibitor of these integrins, cilengitide, was suggested across Phase II trials on recurrent GBMs. Moreover, a presumed more pronounced benefit in tumors with a methylated MGMT promoter has been hypothesized: thus, a multicenter randomized Phase III trial (CENTRIC) has been performed to compare in newly diagnosed MGMT methylated GBMs, the association of cilengitide with radiotherapy and temozolomide with radiotherapy and temozolomide alone. The study results have been negative, as both OS and PFS have not been improved by cilengitide [11]. Ongoing trials are investigating either the combination of anti-VEGF and anti-invasion agents or novel drugs targeting different angiogenesis pathways.
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Editorial

References


