Among the novel treatments for gliomas evaluated in 2012, inhibitors of angiogenesis have undoubtedly raised the most interest. Although mature data are awaited from 2 randomized phase III trials exploring agents with different modes of action (bevacizumab, an antibody to vascular endothelial growth factor [VEGF], and cilengitide, an integrin inhibitor), multiple other targeted agents exploring similar or novel targets are also being explored, including agents inhibiting placental growth factor, fibroblast growth factor, and stromal-derived factor-1. According to a press release by Roche, the registration trial for bevacizumab in the treatment of newly diagnosed glioblastoma, AVAGlio, has reached the primary end point of improving progression-free survival, whereas no mature results for the overall survival end point have been made available. These observations, although preliminary, underscore the urgent need to understand what is happening during treatment with anti-angiogenic agents, in what way such treatments modify tumor biology, and whether there is a risk of promoting an even more malignant tumor phenotype after they escape anti-angiogenic treatment. Altogether, there is little doubt that anti-angiogenic agents can be only cytostatic but are unlikely to represent curative approaches, and innovative sequencing strategies involving radiotherapy and classical cytotoxic chemotherapy remain to be further investigated.

In the present issue of Neuro-Oncology, Piao et al from Dr. John de Groot's laboratory at The University of Texas MD Anderson Cancer Center explored the evolution of resistance to anti-VEGF therapy and compared the ligand-sequestering antibody, bevacizumab, with a small molecule inhibitor of tyrosine kinase receptors, sunitinib.¹ In the U87MG orthotopic human glioma model, bevacizumab doubled median survival, whereas sunitinib had no effect on survival. However, when sunitinib was combined with bevacizumab, survival was increased over the increase achieved with bevacizumab alone. Both agents reduced vascularity in the tumors, but bevacizumab seemed to be more effective in inhibiting vascularity in the periphery of the tumors, compared with sunitinib. There was earlier revascularization in sunitinib-treated tumors than in bevacizumab-treated tumors that was associated with earlier tumor progression. There was, in general, good correlation between vascularization and tumor cell proliferation. Long-term surviving animals showed enhanced tumor invasiveness. Using carbonic anhydrase 9 as a marker of hypoxia, they found that hypoxia was more prominent in control and sunitinib-treated mice than in bevacizumab-treated mice. An increase in CD11b⁺/F4/80⁺ cells was observed earlier in control and sunitinib-treated animals and was, overall, associated with tumor progression and treatment failure.

This is a timely study indicating the potential differences between targeting angiogenic ligands versus angiogenic receptors in glioma models. The potential limitations include the study of only one cell line, which is often not considered to represent the full spectrum of glioma biology. However, this study, as similar previous studies in other glioma models, illustrates that a better understanding of interactions between glioma cells and the tumor microenvironment, specifically in the brain, is required to fully exploit the potential value of anti-angiogenic agents in the treatment of glioblastomas. Specifically, it is important to understand tumor-host cell interactions better: where do infiltrating cells come from, what do they do, and how do they overall contribute to the natural course of disease and to therapy resistance and response?

Michael Weller, Executive Editor, EANO

Reference