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### **Ischemic stroke and intracranial hemorrhage in glioma patients on antiangiogenic therapy.**

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#### **Abstract**

Bevacizumab, a monoclonal antibody against vascular endothelial growth factor (VEGF), recently received FDA approval for recurrent glioblastoma. Additionally, several VEGF receptor (VEGFR) tyrosine kinase inhibitors (TKIs) have entered trials for recurrent glioma. Phase II studies of bevacizumab for recurrent GBM have reported incidents of ischemic stroke (IS) and intracranial hemorrhage (ICH); however, their clinical features and outcomes were not described in detail. We conducted a retrospective study of recurrent malignant glioma patients with radiographically-confirmed IS or ICH while on antiangiogenic therapy. The study population included patients treated between 2005 and 2010 at the National Cancer Institute on four different phase I and II trials of antiangiogenic agents for recurrent malignant glioma, as well as patients receiving bevacizumab off clinical trial during this same period. Eight patients developed IS (50% lacunar) and 14 experienced ICH (79% intratumoral) while on antiangiogenic therapy for malignant glioma recurrence. The median age was 53 years, 17 patients (77%) were men, and 59% had glioblastoma. The frequencies of IS and ICH were 1.9% and 1.9% in bevacizumab trials. None of the patients on VEGFR TKI trials developed IS, while 3.8% experienced ICH. Patients with IS were treated with antiangiogenic agents longer than those with ICH (median, 16.2 vs. 2.6 months,  $P = 0.001$ ). Median survival was 7.8 months after IS and 2.6 months after ICH. The most common IS subtype was lacunar, while most ICHs were asymptomatic and intratumoral. Overall, IS seems to be a complication of prolonged antiangiogenic therapy, while intratumoral bleeds often occur in the setting of tumor progression.

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