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Hemorrhagic and ischemic risks of anti-VEGF therapies in glioblastoma

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Abstract

Glioblastoma (GBM) is one of the most aggressive primary brain tumors, characterized by extensive neovascularization and a highly infiltrative phenotype. Anti-vascular endothelial growth factor (VEGF) therapies, such as bevacizumab, have emerged as significant adjunct treatments for recurrent and high-grade GBM by targeting abnormal tumor vasculature. Despite demonstrated benefits in slowing tumor progression and alleviating peritumoral edema, these agents are associated with notable vascular complications, including hemorrhagic and ischemic events. Hemorrhagic complications range from minor intracranial microbleeds to life-threatening intracranial hemorrhages (ICH). Mechanistically, VEGF inhibition disrupts endothelial function and decreases vascular integrity, making already fragile tumor vessels prone to rupture. Glioma-associated vascular abnormalities, including disorganized vessel networks and compromised blood-brain barrier, further exacerbate bleeding risks. Concurrent use of anticoagulants, hypertension, and genetic predispositions also significantly elevate hemorrhagic risk. In addition to bleeding complications, ischemic events are increasingly recognized in patients receiving anti-VEGF therapy. Reduced vascular endothelial cells (ECs) survival and diminished microvascular density can lead to regional hypoperfusion and potentially precipitate cerebrovascular ischemia. Impaired vasoreactivity and increased vascular resistance, often accompanied by endothelial dysfunction and microvascular rarefaction, contribute to elevated stroke and arterial thrombotic risk. This review synthesizes current evidence on hemorrhagic and ischemic complications arising from anti-VEGF therapy in GBM. We discuss underlying pathophysiological mechanisms, risk factors, and clinically relevant biomarkers, as well as prevention strategies-such as rigorous blood pressure (BP) control and close monitoring of coagulation parameters. We further highlight emerging avenues in precision medicine, including pharmacogenomic profiling and targeted adjunct agents that protect vascular integrity, aimed at mitigating adverse vascular events while preserving therapeutic efficacy. The goal is to optimize outcomes for GBM patients by balancing the benefits of anti-VEGF therapy with vigilant management of its inherent vascular risks. In addition, this study analyzes existing clinical trials of the use of anti-VEGF drugs in the treatment of gliomas using data from the clinicaltirals.gov website.