

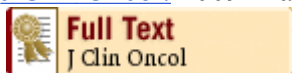


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1: [J Clin Oncol](#). 2009 Mar 30. [Epub ahead of print]



**Edema Control by Cediranib, a Vascular Endothelial Growth Factor Receptor-Targeted Kinase Inhibitor, Prolongs Survival Despite Persistent Brain Tumor Growth in Mice.**

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**PURPOSE:** Recent clinical trials of antivascular endothelial growth factor (VEGF) agents for glioblastoma showed promising progression-free and overall survival rates. However, available clinical imaging does not separate antitumor effects from antipermeability effects of these agents. Thus although anti-VEGF agents may decrease tumor contrast-enhancement, vascularity, and edema, the mechanisms leading to improved survival in patients remain incompletely understood. Our goal was to determine whether alleviation of edema by anti-VEGF agents alone could increase survival in mice. **METHODS:** We treated mice bearing three different orthotopic models of glioblastoma with a VEGF-targeted kinase inhibitor, cediranib. Using intravital microscopy, molecular techniques, and magnetic resonance imaging (MRI), we measured survival, tumor growth, edema, vascular morphology and function, cancer cell apoptosis and proliferation, and circulating angiogenic biomarkers. **RESULTS:** We show by intravital microscopy that cediranib significantly decreased tumor vessel permeability and diameter. Moreover, cediranib treatment induced normalization of perivascular cell coverage and thinning of the basement membrane, as mirrored by an increase in plasma collagen IV. These rapid changes in tumor vascular morphology and function led to edema alleviation-as measured by MRI and by dry/wet weight measurement of water content-but did not affect tumor growth. By immunohistochemistry, we found a transient decrease in macrophage infiltration and significant but minor changes in tumor cell proliferation and apoptosis. Systemically, cediranib increased plasma VEGF and placenta growth factor levels, and the number of circulating CXCR4(+)CD45(+) cells. However, by controlling edema, cediranib significantly increased survival of mice in the face of persistent tumor growth. **CONCLUSION:** Anti-VEGF agents may be able to improve survival of patients with glioblastoma, even without inhibiting tumor growth.

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