Inhibition of glioma angiogenesis and growth in vivo by systemic treatment with a monoclonal antibody against vascular endothelial growth factor receptor-2.

Department of Neurosurgery, University Hospital Hamburg-Eppendorf, 20246 Hamburg, Germany.

Abstract
Using an orthotopic intracerebral model, we investigated whether systemic treatment with DC101, a monoclonal antibody against vascular endothelial growth factor receptor (VEGFR)-2, could inhibit angiogenesis and the growth of human glioblastoma cells in severe combined immunodeficient mice. Intraperitoneal treatment with DC101, control IgG, or PBS was initiated either on day 0 or, in another series, on day 6 after tumor cell implantation, and animals were killed approximately 2 weeks after tumor cell injection. Tumor volumes in animals treated with DC101 were reduced by 59 and 81% compared with IgG and PBS controls, respectively (P < 0.001), when treatment was initiated immediately, and similar results were obtained when treatment started on day 6. Microvessel density in tumors of DC101-treated animals was reduced by at least 40% compared with animals treated with control IgG or PBS (P < 0.01). We observed a reduction in tumor cell proliferation and an increase in apoptosis in DC101-treated animals (P < 0.001). However, in mice treated with DC101, we also noticed a striking increase in the number and total area of small satellite tumors clustered around, but distinct from, the primary. These satellites usually contained central vessel cores, and tumor cells often had migrated over long distances along the host vasculature to eventually reach the surface and spread leptomeningeally. We conclude that systemic antagonization of VEGF-R-2 can inhibit glioblastoma neovascularization and growth but can lead to increased cooption of preexistent cerebral blood vessels. Therefore, a combination of different treatment modalities which also include anti-invasive therapy may be needed for an effective therapy against glioblastoma, and the use of an antibody against VEGF-R-2 may be one effective component.