Focused Ultrasound Enhances Central Nervous System Delivery of Bevacizumab for Malignant Glioma Treatment.

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Abstract

Purpose To demonstrate that magnetic resonance (MR) imaging-monitored transcranial focused ultrasound can enhance the delivery of the antiangiogenic monoclonal antibody bevacizumab into the central nervous system (CNS) for glioblastoma multiforme (GBM) treatment. Materials and Methods All animal experiments were approved by the animal committee and adhered to experimental animal care guidelines. Transcranial focused ultrasound exposure in the presence of microbubbles was used to open the blood-brain barrier (BBB) to enhance bevacizumab penetration into the CNS in healthy and glioma-bearing mice. Bevacizumab concentration was quantitated with high-performance liquid chromatography, and Western blot testing was performed to confirm the specific biologic form in the CNS. Penetration of bevacizumab into brain tissue was estimated in vivo by means of contrast material-enhanced MR imaging and quantitative gallium 68 ((68)Ga)-bevacizumab micro-positron emission tomography, and glioma progression was longitudinally followed with T2-weighted MR imaging. Hematoxylin-eosin staining and cluster of differentiation 31 immunostaining were used to assess morphologic changes and vascular inhibition at histologic examination. The two-tailed Student t test and the Mantel-Cox log-rank test were used for statistical analyses, with a significance level of .05. Results Focused ultrasound significantly enhanced bevacizumab penetration into the CNS by 5.7- to 56.7-fold compared with that in nonexposed brain (both P < .0001). Contrast-enhanced MR imaging indexes correlated with bevacizumab concentration (r = 0.748-0.857) in vivo. Focused ultrasound-enhanced bevacizumab delivery significantly retarded glioma progression, with a significantly increased median survival (median increase in survival time = 135% in the group treated with
bevacizumab and focused ultrasound, P < .0001; as compared with 48% in the group treated with bevacizumab alone, P = .0002). Conclusion Focused ultrasound-enhanced bevacizumab delivery can provide an antivascularization normalization effect to suppress glioma. (©) RSNA, 2016 Online supplemental material is available for this article.

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