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Blood-brain barrier disruption with focused ultrasound enhances delivery of chemotherapeutic drugs for glioblastoma treatment.

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Abstract

PURPOSE: To demonstrate the feasibility of using focused ultrasound to enhance delivery of 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU) to glioblastomas in rats with induced tumors and determine if such an approach increases treatment efficacy.

MATERIALS AND METHODS: All animal experiments were approved by the animal committee and adhered to the experimental animal care guidelines. A 400-kHz focused ultrasound generator was used to transcranially disrupt the blood-brain barrier (BBB) in rat brains by delivering burst-tone ultrasound energy in the presence of microbubbles. The process was monitored in vivo by using magnetic resonance (MR) imaging. Cultured C6 glioma cells implanted in Sprague-Dawley rats were used as the tumor model. BCNU (13.5 mg/kg) was administered intravenously and its concentration in brains was quantified by using high-performance liquid chromatography. MR imaging was used to evaluate the effect of treatments longitudinally, including analysis of tumor progression and animal survival, and brain tissues were histologically examined. Methods including the two-tailed unpaired t test and the Mantel-Cox test were used for statistical analyses, with a significance level of .05.

RESULTS: Focused ultrasound significantly enhanced the penetration of BCNU through the BBB in normal (by 340%) and tumor-implanted (by 202%) brains without causing hemorrhaging. Treatment of tumor-implanted rats with focused ultrasound alone had no beneficial effect on tumor progression or on animal survival up to 60 days. Administration of BCNU only transiently controlled tumor progression; nevertheless, relative to untreated controls, animal survival was improved by treatment with BCNU alone (increase in median survival time [IST(median)], 15.7%, P = .023). Treatment with focused ultrasound before BCNU administration controlled tumor progression (day 31: 0.05 cm(3) + or - 0.1 [standard deviation] vs 0.28 cm(3) + or - 0.1) and improved animal survival relative to untreated controls (IST(median), 85.9%, P = .0015).

CONCLUSION: This study demonstrates a means of increasing localized chemotherapeutic drug delivery for brain tumor treatment and strongly supports the feasibility of this treatment in a clinical setting.

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