The Setting

Malignant glioma—glioblastoma multiforme (GBM) in its fullest expression—remains one of the deadliest and most frustrating neoplasms to manage. Regardless of diagnostic nuance and specific treatment, the ultimate outcome is nearly always death, usually within 18 months. This most unfortunate but undeniable fact has not changed significantly since I was introduced to this tumor as a medical student in the 1960s (1,2).

Since the advent of x-ray computed tomography (CT) in the 1970s, the diagnosis of malignant gliomas has not been a problem. Symptoms at presentation are protean, but when they become sufficient to justify an imaging study, the tumor and diagnosis are usually obvious. The average size of a GBM at presentation is greater than 3 cm in diameter, and, with rare exceptions, the tumors are easily detected and specifically diagnosed on the basis of the initial imaging study. One rarely “misses” a GBM, even with non–contrast-material-enhanced CT, much less with contrast-enhanced magnetic resonance imaging. Furthermore, the pathologic diagnosis is also usually straightforward, with the classic pathologic features of vascular proliferation and necrosis being present in more than 80% of cases at open or closed biopsy (3).

That is not to say that we have not learned more about these unique tumors. While malignant gliomas are uniformly deadly, they do show molecular, genomic, and advanced imaging heterogeneity that define subtypes related to survival time and possibly to response to different treatment regimens (4). Particularly pertinent to this Science to Practice article are the tumors that overexpress angiogenic factors, such as vascular endothelial growth factor (VEGF), and that are characterized by aggressive angiogenesis. GBMs overexpressing VEGF have been associated with shorter survival after standard treatment but have been shown to preferentially respond...
to antiangiogenic agents (5). However, the treatment response is only temporary and is thought to be compromised by “vascular normalization,” a self-restricting result of anti-VEGF treatment.

**The Science**

Liu and colleagues (6), in the companion scientific article, have proposed and tested in a preclinical mouse model a new treatment method for GBM that builds on what we now know about molecular GBM subtypes and tumor-specific treatment regimens. Most chemotherapeutic drugs have limited access to brain tissue because of the blood-brain barrier (BBB), which limits passage of larger molecular weight hydrophilic compounds, which include most chemotherapeutic agents. Disruption of the BBB could improve drug delivery to neoplastic tissue. The authors demonstrate temporary and spatially selective BBB disruption by a combination of focused ultrasound and intravenously injected microbubbles that permits delivery of higher concentrations of chemotherapeutic drugs to targeted areas. In this particular report, the chemotherapeutic drug is an antiangiogenic drug, bevacizumab, a monoclonal antibody to the VEGF-A isoform that is overexpressed in many clinical GBMs and in this particular mouse tumor model. Using the well-documented mouse brain tumor xenograph model U87, which overexpresses VEGF, the authors show that intravenous bevacizumab delivered in conjunction with focused ultrasound and microbubbles results in higher concentrations of the drug in the focused ultrasound/tumor bed and, compared with control treatment, restricts tumor growth and prolongs survival.

The method involves applying carefully calibrated high-energy focused ultrasound to the tumor bed in conjunction with the intravenous injection of the microbubble contrast agent SonoVue. These microbubbles are ruptured by the ultrasound energy and increase the direct ultrasound effect on vascular endothelium, transiently disrupting the BBB in the ultrasound field. Disruption of the BBB allows passage of much more (one to two orders of magnitude) bevacizumab into the focused ultrasound field, which in this case is the tumor bed. Adverse side effects were not reported.

**The Practice**

**Clinical use:** The general concept of future clinical application is relatively straightforward. The microbubble compound is intravenously injected while focused ultrasound is delivered with image-guided techniques to a previously diagnosed GBM. Simultaneously, bevacizumab is injected intravenously. The microbubble compound SonoVue is approved for use as a diagnostic contrast agent in Europe and the United States. Open and closed (with or without craniotomy) focused ultrasound methods have been described for hyperthermic treatment of brain and other tumors and might be modified for this purpose (7). Bevacizumab has been shown to inhibit human GBM growth and to prolong tumor-free survival and is in clinical trials (5). A phase I clinical trial seems technically feasible.

**Future opportunities:** The concept of BBB disruption by focused ultrasound could be applicable to many chemotherapeutic agents. In fact, these same authors have previously applied the microbubble/focused ultrasound technique to another chemotherapeutic agent, Carmustine, in a different mouse glioma model and showed improved tumor response (8). Furthermore, one could envision treating one part of a tumor (nonnecrotic) with BBB disruption and chemotherapy and another part of the tumor (necrotic) with ablative hyperthermia.

**Challenges:** A question related to all tumor models, but particularly xenograft tumor models, is their comparability to human GBM. Although xenograft tumors are commonly used and have been shown to have similarities to human tumors, there are well-known dissimilarities, including shorter doubling times, different vascular and stromal elements, and the host immune response (9).

In the accompanying and previous reports, the authors state that there were no adverse effects of BBB disruption with use of this method within the prescribed safety limits. However, they monitored these laboratory animals only for gross neurologic changes and did not rigorously evaluate more subtle behavioral changes. BBB disruption in human patients has been accomplished by using focused ultrasound and other methods, including the intraarterial injection of hyperosmolar agents (10). Adverse events have been reported, with seizures occurring in 5% of 300 treated patients and one case of lethal edema.

Clinical focused ultrasound delivery methods will have to be carefully defined. Should it be performed with open or transcranial delivery? Most GBMs are large, even after gross total removal, and large-volume focused ultrasound remains a technical challenge. Safety limits must be carefully defined—high enough to open the BBB but not sufficient to raise tissue temperature to lethal levels, as done with ablative focused ultrasound.

What part of the tumor should be insonated and when? Should all or only a portion of the tumor and surroundings be treated with BBB disruption and chemotherapy? The delivery concentration and therapeutic effect of bevacizumab are modulated by the vascular state of the tumor. Should the components of the tumor that are only necrotic, contrast enhancing, and/or T2 intense be treated similarly? Should one treat the vascularly “normalized” part of the
tumor the same as “nonnormalized” components?

Since the therapeutic dose and effect of many, if not most, chemotherapeutic agents might be improved by using this technique, which drugs should be delivered in this fashion? For bevacizumab, it is important to know if the tumor is VEGF positive. This is currently determined through immunohistologic analysis with a limited number of biopsy sites, which may not reflect the spatial heterogeneity of the molecular phenotype. How do other concomitant therapies, such as radiation therapy, affect the efficacy and safety of this treatment?

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