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# Setting the stage: local delivery of cytoreductive agents for the treatment of glioblastoma

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Despite decades of intense research, the prognosis for glioblastoma (GBM) is unacceptably dismal. Nevertheless, modest measurable progress has been made on behalf of patients diagnosed with the condition over the past 20 years. In a population-based review of the Surveillance, Epidemiology, and End Results (SEER) Program database of the National Cancer Institute comprising 19 674 cases of GBM in patients ≥20 years of age, Darefsky et al found that 2-year survival increased from 7% in cases diagnosed between 1993 and 1995 to 17% in cases diagnosed between 2005 and 2007.[1] The investigators attributed this improvement to what they characterized as "the temozolomide era"—the addition of systemic temozolomide, beginning in the late 1990s, into an aggressive package of multimodality therapy combined with resection and radiotherapy—although they acknowledged the contributing influence of other treatment advances such as the increased extent of resection. At my own institution, the Hermelin Brain Tumor Center at Henry Ford Hospital in Detroit, Michigan, 2-year survival in patients with GBM has increased more than 3-fold, from 8.1% in 1995 to 29.8% in 2008, with ever more patients now enrolled in clinical trials and being treated by a multidisciplinary tumor board and receiving personalized therapies based on molecular assessments of various cancer-related genes.[2]

GBM seldom metastasizes but typically spreads contiguously, with invasive tumor cells often being found several centimeters away from the enhancing tumor mass, even on the contralateral side of the brain.[3] Thus, advanced surgical techniques—such as intraoperative and functional MRI, real-time brain mapping, fluorescence-guided surgery, and stereotactic localization—will never be able to fully cure the disease. With the blood-brain barrier (BBB) standing as a difficult obstacle for systemic chemotherapy, research into strategies for BBB disruption, while intriguing,[4] has not yet yielded substantive results. In the meantime, our continuously increasing molecular understanding of GBM has not yet been translated into effective treatments during the temozolomide era.[5]

The possibility of treatment breakthroughs is now on the horizon, with new means of local delivery for both conventional and novel cytoreductive agents to the brain. Local delivery, which is not limited by the BBB, might prove safer and more effective than systemic delivery. Moreover, while the temozolomide era continues, the interim between surgical resection and the start of chemoradiation could be used for immediate local treatment of residual and rapidly dividing tumor cells in addition to current standard therapy.

The purpose of this journal supplement to *Neuro-Oncology* is to detail the state-of-the-art strategies for local delivery of cytoreductive agents to the brain for treatment of newly diagnosed GBM. In the first of these expert review articles, Vogelbaum and Aghi explain recent developments in convection-enhanced delivery (CED), the use of implanted catheters through which cytoreductive agents can be delivered by means of continuous, low-pressure bulk flow. Pressure-driven CED promises to significantly enhance drug penetration to distant residual cells in the extracellular space of the brain. In the second article, Wait et al, in turn, evaluate the history and outcomes to date of polymeric drug delivery in the brain. Also developed in the 1990s, the implantable BCNU wafer is, like temozolomide, one of the few cytoreductive therapies for GBM for which there is level II evidence proving efficacy.[6] Finally, in the third article, Kane et al analyze different types of gene therapy as well as the different gene-delivery methods. They provide a primer on the complex advances in this field, emphasizing the positive safety outcomes in clinical trials of gene therapy delivered by various carriers.

As physician editor of this supplement, I want to thank the expert authors, who are luminaries in their field, for their incisive contributions. I also want to thank *Neuro-Oncology* for being willing to publish this timely review of local delivery systems for treatment of GBM. Whether or not we have the right cytoreductive agents, none will succeed at vastly improving survival times for GBM without achieving sufficient penetration of the brain to reach residual GBM cells after the tumor has been resected. To that end, I urge my colleagues to

preferentially support research and clinical trials of these emerging delivery strategies.

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