

State-of-the-art Therapy for Glioblastoma Multiforme

a report by

Henry S Friedman, MD

James B Powell Jr Professor of Neuro-oncology, Dukes University Medical Center, Durham

DOI: 10.17925/OHR.2007.00.2.103

The treatment of patients with glioblastoma multiforme (GBM) is considered to be a palliative venture with no hope of cure. Traditionally, patients are treated with maximal surgical resection based on the premise that, although surgery is not a curative procedure, a major resection leads to longer survival and better quality of life.¹ Radiotherapy increases the duration of survival, but again is not a curative intervention.² The role of chemotherapy, specifically focusing on a foundation of chloroethylating agents such as carmustine (BCNU) or lomustine (CCNU), has been controversial with an equal number of clinicians arguing in favor or against this treatment. Meta-analysis makes it clear that there is a small increase in median survival associated with the addition of these agents, but a consensus was never reached regarding their use.³

Unfortunately, the underlying assumption of virtually all clinicians that GBM is not a curable tumor led to a wide spectrum of interventions utilized in the community to treat these patients. Many patients received a biopsy rather than a major resection of their tumor. Despite the lack of evidence supporting whole-brain versus focal radiotherapy, some patients received (or still receive) whole-brain radiotherapy with the associated increased morbidity. Finally, community and academic physicians chose to not use chemotherapy without a firm foundation of data to support withholding it.

A positive step forward started with the synthesis and evaluation of temozolomide and subsequent phase I and II trials with this methylating agent in the UK. Temozolomide was shown to have activity in phase I trials in two patient populations: those with malignant glioma or those with melanoma.⁴ Subsequent phase II trials in the UK confirmed this activity,⁵ leading Schering Plough to license the drug for studies in the US. Following phase I trials in adults and children, a pivotal registration trial in patients with GBM—and also anaplastic astrocytoma in a separate trial—and a trial of newly diagnosed patients with GBM with residual disease following initial surgical intervention or biopsy intervention were initiated. The first published study by Friedman et al.⁶ demonstrated the profound activity of temozolomide in patients with newly diagnosed GBM, with a response rate exceeding 50%. Although the registration trial for patients with first-relapse GBM demonstrated a near tripling of the six-month progression-free survival, concerns voiced by the US Food and Drug Administration (FDA) regarding this as a legitimate end-point prevented the approval of temozolomide for this indication.⁷ However, the one-arm study evaluating temozolomide in the treatment of patients with first-relapse anaplastic astrocytoma led to an accelerated approval for this agent.⁸

Roger Stupp took the next step forward by building on the results of the previous studies of temozolomide. A one-arm trial was initiated of

65 patients who received surgery then radiation with daily temozolomide, followed by six cycles of the traditional 'drug five days a month.'⁹ These results showed a provocative survival curve, leading to a randomized phase III trial in patients with newly diagnosed GBM. The results confirmed the benefit of temozolomide, which produced a modest increase in survival for patients receiving this agent.¹⁰ Overnight, temozolomide became the global standard of care. Ironically, an agent producing a similar increase in survival—notably Gliadel wafers®, which release BCNU into a tumor cavity following their implantation—has not been as universally accepted.¹¹ Although this may have initially reflected concerns with toxicity—due to a lack of appreciation of the need for a watertight dural seal following placement of these wafers—and the initially unfavorable cost (at least in the US), it is now clear that both of these problems have been addressed and the use of this agent appears to be increasing.

Currently, the problem faced in the field is the continued belief that patients with GBM will die and, therefore, our efforts are merely palliative. Accordingly, patients are treated routinely in the community with surgery followed by radiation and temozolomide, then by temozolomide with virtually no hope of long-term survival. It is absolutely ludicrous to believe that any malignancy, particularly one as aggressive as GBM, can be cured with single-agent chemotherapy. Unfortunately, the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC) have combined to conduct an extremely large trial that will encompass over 1,100 patients with GBM who receive surgery followed by radiation plus temozolomide followed by one of two dose schedules of temozolomide. The underlying scientific hypothesis is that the prolonged temozolomide will deplete O-6-methylguanine-DNA methyltransferase (MGMT) allowing enhancement of temozolomide activity with an increased overall survival of patients treated on the dose-intense arm. However, single-agent chemotherapy is, again, unlikely to



Henry S Friedman, MD, is the James B Powell Jr Professor of Neuro-oncology at Dukes University Medical Center, Durham, North Carolina. He is also Deputy Director of The Preston Robert Tisch Brain Tumor Center at Duke. Dr Friedman is internationally recognized for his work as an educator, clinician, and laboratory/clinical investigator in both pediatric and adult brain and spinal-cord tumors. He has published over 350 articles in peer-reviewed professional journals. He trained in neuro-oncology at Duke University Medical Center, and

joined the faculty at that institution in 1983. Dr Friedman received his MD from Upstate Medical Center in Syracuse, New York, in May 1977, and stayed at that institution for pediatric and pediatric hematology-oncology training.

E: fried003@mc.duke.edu

make any kind of major progress in the treatment of glioblastoma or any other malignancy, and this may well be a waste of patient resources without achieving any great gain. Nevertheless, this standard of care persists because there is a concern that there are no other active agents, and the belief that only patients on clinical trials should receive agents that are not approved by the FDA to counter a specific malignancy.

Although the community standard of care in the US for oncology patients is to utilize commercially available agents in an off-label setting when data support their use, in many academic neuro-oncology programs there is major resistance to this approach. This problem can be dealt with in two ways. The first is to design clinical trials using multiple agents in the treatment of GBM. The study by La Rocca et al. is a step in the right direction since it evaluates the use of surgery with placement of Gliadel wafers followed by radiation and temozolomide, followed by temozolomide as a single agent in the treatment of patients with newly diagnosed GBM.¹²

An additional series of clinical trials focusing on patients with recurrent GBM have evaluated the activity of bevacizumab and irinotecan. Although initially there was concern that bevacizumab was merely producing a steroid-like effect, the long duration of follow-up and the marked progression-free survival at six months makes it clear that this combination has the most activity of any regimen identified to date in the treatment of this tumor.^{13,14} Additionally, the study conducted under the auspices of Genentech and recently presented at the 2007 Society of Neuro-Oncology meeting indicates that Avastin alone has particular activity, although it appears to be increased when combined with irinotecan. There is no question that FDA approval will be sought for these regimens for recurrent GBM, and studies that should open within the next year will evaluate the role of Avastin in the treatment of patients with newly diagnosed GBM. This is a far more optimistic approach than simple dose escalation of temozolomide as detailed above.

Patients not on a clinical trial can also be treated with off-label commercially available agents, particularly if other studies will evaluate these agents in formal clinical trials. Therefore, we are not slowing the field's progress, but offering hope to patients who are not on a trial. As detailed above, although phase III trials evaluating bevacizumab in newly diagnosed patients will be forthcoming, there is no reason why patients

who are not protocol-eligible cannot receive this as part of their standard of care. We follow this strategy of using off-label commercially available drugs at Duke and, between 2003 and 2006, 85 patients were treated with surgery, Gliadel wafers (if anatomically appropriate), and radiation therapy with concomitant temozolomide, followed by a rotation of temozolomide, CCNU, and irinotecan. These results are promising and prevent the all-too-frequent occurrence that only patients on clinical trials are offered optimistic therapy.¹⁵ We now routinely include bevacizumab and irinotecan in the treatment of all newly diagnosed patients with GBM who are not enrolled on clinical trials.

An additional concern that has arisen following the universal acceptance of temozolomide has been the role of MGMT—also known as O6-alkylguanine DNA alkyltransferase—in making decisions regarding the use of temozolomide. A series of clinical studies have clearly demonstrated the role of this protein in predicting response to temozolomide. Friedman et al.⁶ showed this first in the upfront study of patients with newly diagnosed GBM. Roger Stupp built on this with subsequent trials further defining the relationship between MGMT and temozolomide. Unfortunately, it is not an all-or-nothing relationship, particularly when using the promoter methylation assay. It is clear that any recommendations to use or not use temozolomide based on this assay are inappropriate. Maxwell et al.¹⁶ clearly demonstrated that even in a situation where the methylation assay actually showed a lack of methylation of the promoter, there is still a population of cells that do not stain for MGMT and, therefore, are likely to be sensitive to temozolomide. The appropriate recommendation when the MGMT promoter is not methylated is not to withhold temozolomide, but rather to use it while including additional agents that will not be susceptible to this protein. Of course, we argue that additional agents should always be used, and never rely on temozolomide alone as a single agent.

Patients with GBM are not universally incurable, with an ever-increasing, albeit small, fraction of patients who appear to survive the disease. The wisdom of utilizing multiple chemotherapeutic agents with non-overlapping toxicity and independent mechanisms of action unequivocally is producing an ever-increasing cohort of patients for whom GBM is not a terminal event. Reliance on a single agent, whether temozolomide or anything else, is nihilistic, inappropriate, and clearly going to be unsuccessful. ■

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