Current Management of High-grade Astrocytic Neoplasms—Small but Tangible Progress

a report by
Renato V La Rocca, MD

Oncologist and Director, Kentuckiana Cancer Institute, Kentucky

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The last five years have seen an evolution in the management of high-grade astrocytic tumors comparable in scope yet greater in magnitude to that of the prior 40 years. This is thanks to the convergence of three factors: the introduction of an oral agent with antitumor activity beyond the blood–brain barrier and modest systemic toxicity (temozolomide); the demonstration through a well-conducted randomized trial of the superiority of multimodality therapy; and the fact that we now stand on the threshold of additional progress through key advances in translational biology, which, in many cancers, is providing new targets for therapeutic intervention.

Astrocytic tumors have long been the bane of neurosurgeons, radiation therapists, and neuro-oncologists. Although they account for only 2.3% of all cancer-related deaths in the US,[1] little if any substantial progress in brain imaging and treatment had been made until the first years of this millennium. Characteristics of high-grade glial tumors compared with other cancers are its unique location, robust invasive and angiogenic capabilities without a significant propensity to metastasize outside of the central nervous system (CNS), and the profound histological and molecular heterogeneity within tumor specimens.

Advances in the Management of Glioblastomas—Multimodality Strategies

In 2003, a phase III study in 240 newly diagnosed patients with surgically resectable malignant gliomas—including 207 with glioblastoma multiforme (GBM)—compared surgery plus radiotherapy and placebo wafers with surgery plus radiotherapy and the addition of 3.8% bischloroethyl nitrosourea (BCNU, carmustine) wafers (Gliadel wafers) into the tumor bed. The study demonstrated a modest, albeit significant, prolongation of survival in the latter group (13.9 versus 11.6 months).[2] Long-term follow-up of this study showed that the survival advantage with BCNU wafers was maintained at one, two, and three years, and was statistically significant (p=0.01) at three years compared with placebo, although the absolute number of patients evaluated at this latter time-point was quite small.[3]

Perhaps the most significant advance in the management of glioblastomas emanates from the work of Stupp et al.[4] who, in a safety and efficacy study, randomized 573 patients with newly diagnosed glioblastoma from 85 centers, primarily in Europe, to radiotherapy alone or to radiotherapy plus concomitant temozolomide followed by monthly temozolomide for six cycles. At a median follow-up of 28 months the median survival in the radiotherapy group alone was 12.1 months compared with 14.6 months in the group receiving both treatment modalities (p<0.001). The two-year survival rate was 10.4% with radiotherapy alone versus 26.5% with radiotherapy and temozolomide. The results of this study produced level 1A evidence for the benefit of this combined modality treatment in initially diagnosed patients, and was incorporated into the new National Comprehensive Cancer Network (NCCN) guidelines for CNS tumors in 2005.

Thus, as a next logical step, a fusion of these two prior studies was evaluated in a phase II setting in patients with newly diagnosed, high-grade GBM undergoing resection with BCNU wafer insertion followed by the combination of radiotherapy plus temozolomide. Early interim data have been presented in abstract form.[5] The study end-points include survival and progression-free survival (PFS). Of 35 patients enrolled so far, 34 were diagnosed with GBM. At median follow-up of 10.4 months, 25 patients had documented recurrence and 19 patients had died. Six patients remain on active treatment. The one-year survival rate is 64%, and median survival is 18.6 months. These early data suggest that combination therapy with BCNU wafers followed by therapy plus temozolomide may be an effective regimen in patients with initial high-grade resectable malignant gliomas, although randomized trials will ultimately be needed to assess the efficacy of this treatment modality. Other treatment modalities that have been investigated for the treatment of high-grade astrocytic tumors—especially in terms of targeting disease localized to the surgical bed or the surrounding area—have included stereotactic radiosurgery and brachytherapy. A randomized trial conducted by the Radiation Therapy Oncology Group (RTOG) compared post-operative conventional radiotherapy plus systemic BCNU alone or preceded by stereotactic radiosurgery—including both linear accelerator or gamma-knife—in patients with GBM (>4cm tumor size). The results of the trial were disappointing with no improvement in local control or survival with stereotactic radiosurgery.[6]

The US Food and Drug Administration (FDA) has recently approved GliaSite, a novel brachytherapy device, to provide local post-operative irradiation to high- grade gliomas. However, to date, no efficacy trials have been conducted with the system. In a retrospective, multi-institutional analysis, median survival— measured from the date of GliaSite placement—was 35.9 weeks for patients with an initial diagnosis of GBM. The patient population consisted of patients with recurrent high-grade gliomas who had previously undergone resection and had received external beam radiotherapy as part of their initial treatment. Following surgical debulking of the recurrent lesion, an expandable balloon catheter (GliaSite) was placed in the tumor cavity. Although re-irradiation of malignant gliomas with the GliaSite system appeared to

provide a modest survival benefit, it is difficult to assess the value of any survival without the benefit of a control group.[7]

Convection-enhanced delivery (CED) of toxins to the tumor site is a new treatment modality under investigation for malignant gliomas. It was developed as a method to treat brain tumors by circumventing the normal limitations imposed by the blood–brain barrier. CED involves the stereotactically guided implantation of delivery catheters directly into the residual tumor or around the resection cavity to facilitate the local delivery by high-flow micro-infusion of the targeted toxin to tumor cells. A combined summary of three phase I clinical trials investigating the use of cintredekin besudotox—a recombinant protein consisting of interleukin-13 (IL-13) and a truncated form of *Pseudomonas exotoxin*—delivered via CED in the treatment of recurrent malignant glioma following tumor resection, demonstrated an overall median survival after treatment of 45.9 weeks.[8] The Phase III Randomized Evaluation of Convection Enhanced Delivery of IL13-Pe38qqr with Survival Endpoint (PRECISE) Trial was designed to compare CED of cintredekin besudotox to treatment with the BCNU wafers in 294 patients with first recurrence or progression of GBM. Unfortunately, the study was stopped in December 2006 after the efficacy end-point of a statistically significant difference in overall survival was not met. Indeed, the median survival in the CED arm was 36.4 weeks, while that of the BCNU wafer arm was 35.3 weeks. An NCI-sponsored phase I trial is currently evaluating CED of 131I-chTNT-1/B, a chimeric tumor necrosis therapy antibody attached to the radioisotope iodine 131 in malignant glioma. Although CED is a promising alternative for targeted delivery, it remains a complex, interdisciplinary technique that needs further investigation to optimize catheter positioning and drug distribution.

Molecular Targets and Prognostic Factors

Turning to recent advances in the genomic analysis of glioblastoma, four molecular markers are currently being explored. First is the identification of loss of the chromosome 1p/19q in anaplastic oligodendroglioma as a predictor of response to chemotherapy—particularly PCV (procarbazine, CCNU [chloroethylnitrosourea, lomustine], and vincristine). The initial results, published by Cairncross et al. in 1998,[9] led to two randomized clinical trials. The first—European Organization for Research and Treatment of Cancer (EORTC) 26951—evaluated radiotherapy versus radiotherapy followed by PCV in patients with newly diagnosed anaplastic oligodendroglioma or anaplastic oligo-astrocytomas.[10] The second (RTOG 94-02) evaluated PCV given prior to radiotherapy.[11] Both studies demonstrated that the addition of PCV improved PFS without impacting on overall survival (OS). Although chromosome-1p/19q loss does predict chemosensitivity, it did not identify patients who have a better outcome after adjuvant chemotherapy. Moreover, it became apparent that patients with the combined chromosomal 1p/19q loss have a better outcome after radiotherapy compared with patients whose tumor does not contain this chromosomal aberration. At a molecular level, up to 50% of glioblastoma specimens express dysregulated epidermal growth factor receptor (HER1/EGFR).[12] This observation has spurred interest in the use of the small molecule HER1/EGFR-targeted therapy agents such as erlotinib and gefitinib. Initial phase II studies evaluating gefitinib failed to demonstrate significant objective tumor regressions, with a six-month PFS of only 13% in 53 patients with recurrent glioblastoma.[13]

In contrast, the data relating to erlotinib initially appeared somewhat more promising in one study of 31 patients with recurrent glioblastomas, in which six patients achieved a partial response and the six-month PFS was 26%.[14,15] Of note is that these authors could not determine any correlation between response and EGFR expression or amplification within the tumor specimens. Also, a second phase II study of 30 patients treated with erlotinib failed to result in any objective responses or six-month PFS.[16] Unfortunately, a recent EORTC trial comparing erlotinib with either temozolomide or BCNU in 110 patients with recurrent glioblastoma failed to demonstrate a benefit of the oral targeted therapy with respect to six-month PFS or 12-month survival.[17] Optimal dosing of these oral agents, especially while patients are taking enzyme-inducing anti-epileptics or drugs with similar pharmacological effects, may be a significant confounding variable in determining their true clinical efficacy.[18]

> MGMT promoter methylation may be predictive of outcome to multimodality treatment in glioblastoma.

Another molecular target of some promise in the management of patients with GBM is transforming growth factor beta (TGF-B). Not only does it stimulate cell migration, invasion, and angiogenesis, but it also appears to play an important role in the disruption of afferent and efferent immune responses.[19] Several *in vitro* systems, as well as rodent glioma models, delineate the potential therapeutic impact of TGF-B antagonism, employing not only antisense strategies, but also specific TGF-B receptor kinase antagonists. In particular, the use of such agents in conjunction with vaccines, or perhaps novel approaches of cellular immunotherapy, bears further study. Another molecular marker of interest is the O6-methylguanine-DNA methyltransferase (MGMT) promoter gene, also known as O6-alkylguanine-DNA alkyltransferase or AGT. The gene itself expresses alkyltransferase, which plays a role in resistance to alkylating and methylating agents. Methylation of this gene disrupts the expression of alkyltransferase and thus renders the cell more susceptible to alkylating and methylating chemotherapy agents such as temozolomide. Hegi et al. analyzed tissue from newly diagnosed patients with glioblastoma enrolled into the EORTC 26981 trial, and documented a significant correlation between MGMT methylation and outcome from treatment.[20] Methylation of the MGMT promoter was demonstrated in 45% of 206 tumors analyzed, and this was associated with a 46% survival rate at two years compared with only 13.8% in those patients with non-methylated promoter status.[20] Although the preliminary conclusion from this translational study is that MGMT promoter methylation may be predictive of outcome to multimodality treatment in glioblastoma, validation from additional prospective studies is required.

A novel oral protein kinase C inhibitor that initially appeared to have activity in recurrent glioblastoma was enzastaurin. This agent, an oral inhibitor of PKCβ and PI3K/AKT pathways, is well tolerated, possesses antiangiogenic properties in pre-clinical models, and induces tumor cell apoptosis.[21] Enzastaurin is currently being evaluated in phase II trials for

the treatment of patients with recurrent high-grade gliomas. Initial results in 87 evaluable patients with recurrent high-grade gliomas showed that enzastaurin treatment was well tolerated and objective radiographic responses were seen in 22% of patients with GBM. The exposure to enzastaurin was significantly lower in patients treated with enzyme-inducing antiepileptic drugs (EIADs).[22] Enzastaurin also appears to be safe in conjunction with radiation therapy and temozolomide in patients with newly diagnosed GBM.[23] GBM is highly angiogenic, and vascular endothelial growth factor (VEGF) is amplified in most GBM tumors.[24] Over the last three years, there has also been an evolution in the understanding of the 'brain tumor stem cell.' If the concept of a brain tumor stem cell proves to be a real entity, identifiable perhaps by CD-133 expression, and correlated with a significant angiogenic effect associated with VEGF expression and production, this could confirm an important role for antiangiogenic therapy in this cancer.[25] This prompted the evaluation of the recombinant humanized anti-VEGF monoclonal antibody bevacizumab in patients with malignant gliomas. A recent phase II trial studied the effect of bevacizumab in combination with the cytotoxic agent irinotecan in patients with recurrent high-grade astrocytic neoplasms.[26] The investigators demonstrated a radiographic response rate of 63% with the combination therapy and six-month overall survival was estimated at 72%. A randomized phase II study in patients with recurrent glioblastomas evaluating bevacizumab alone versus bevacizumab with irinotecan was recently completed and the results are anxiously awaited . Additional agents with antiangiogenic properties such as the multitargeted agents sorafenib and sunitinib are also being investigated in malignant gliomas.[27,28]

> Multitargeted therapy is a necessity to manage high-grade brain tumors optimally.

Conclusion

Significant advances are being made in the understanding of the biology of high-grade gliomas, which are contributing to the development of promising targeted therapies and treatment modalities. Over the last couple of years, there has been an evolution in the understanding of the 'brain tumor stem cell.' If the concept of a brain tumor stem cell proves to be a real entity identifiable by CD-133 expression, and if this correlates with a significant angiogenic effect associated with VEGF expression and production, it opens new possibilities for targeted therapy.[27] Multitargeted therapy is a necessity to manage high-grade brain tumors optimally. The potential of quadruple multimodality therapy for the management of brain tumors, which includes surgery, radiotherapy, systemic therapy, and localized chemotherapy, needs to be further investigated. Furthermore, with the promising results seen with bevacizumab, there is the possibility of a fifth modality—an antiangiogenesis inhibitor. ■

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