Recent Advances in the Treatment of Gliomas – Comprehensive Brain Tumor Center

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ABSTRACT

Gliomas are a class of primary brain tumors arising from the supporting structures of the brain, the astrocytes and oligodendrocytes, which range from benign lesions to its most malignant form, the glioblastoma. Treatment for these lesions includes maximal surgical resection, radiotherapy, and chemotherapy. Recently, novel therapies such as immune modulatory therapies and electrical field treatment of the most malignant form, the glioblastoma, have shown promise in improving survival. We will review recent advances in clinical trials, explore the role of multimodal care in brain tumor therapy, as well as explore advances in molecular biology and nanotechnology which offer new hope for treatment of this class of disease.

KEYWORDS: glioblastoma, immunotherapy, tumor treating fields, nanotechnology, drug delivery

INTRODUCTION

Gliomas are a class of tumors which arise from the supporting structures of the brain, astrocytes and oligodendrocytes. They range in behavior from benign lesions with distinct borders such as juvenile pilocytic astrocytomas, curable with surgical resection alone, to more diffusely infiltrative cancerous lesions, astrocytomas, oligodendrogliomas, and glioblastoma, all uniformly lethal in a matter of several to many years. In this brief review, we will focus on the most lethal of these, the glioblastoma (GBM).

GBM is the most devastating primary malignancy of the central nervous system in adults. Currently, standard treatment consists of maximal safe surgical resection or a diagnostic biopsy, followed by radiotherapy (60 Gray) with concomitant daily temozolomide chemotherapy, followed by maintenance treatment with temozolomide for 6- to12 months[1]. However, most patients will die within 1 to 2 years. Median progression-free survival from diagnosis of 6.2 to 7.5 months and median overall survival from diagnosis of 14.6 to 16.7 months have been reported in clinical trials[1-4]. The reported 2- and 5-year survival rates are 27% and 10%, respectively. During the last decade, all attempts to improve outcomes for patients with glioblastoma have failed when evaluated in large randomized trials[2-6]. Most recently, the development of electric current loco-regional antimitotic therapy ("tumor-treating fields") led to the first reported survivals exceeding 20 months[7].

In the United States alone, 12,000 new cases of GBM are diagnosed each year[8]. One reason cited for the failure to improve survival has been the presence of a robust blood-brain barrier within the tumor, which impedes delivery of traditional cytotoxic and novel molecular therapies[9]. Most chemotherapeutic agents are hydrophilic, and do not penetrate the blood brain barrier well. Attempts to deliver chemotherapeutic molecules into the brain have included both osmotic, chemical, and ultrasound mediated opening of the blood brain barrier to improve drug delivery, but none have improved clinical outcomes[10]. A novel method to bypass this barrier, (i.e., convection enhanced delivery), met with success in delivering high drug concentrations of hydrophilic drugs to brain tumors and led to several clinical trials. However, convection-enhanced delivery has not yet been associated with improved clinical response. This failure has been ascribed to inhomogeneous delivery of the drug to the entire tumor, as well as difficulty in modeling the bulk flow of infusate :drug to the tumor volume[11,12].

CARING FOR THE GLIOMA PATIENT – THE ROLE OF THE MULTIDISCIPLINARY CLINIC (MDC)

The care of the patient with glioma is nuanced and complex. Patients with a new diagnosis of glioma are often confused and required to make complex decisions about their care in a relatively short period. Unfortunately, the knowledge required to guide a patient through that decision making process is usually beyond the ability of the primary care provider or even the general medical or radiation oncologist. This is where a modern MDC staffed with neuro-oncologists, neuro-oncological surgeons, radiation therapists, and their support teams are crucial.

At an initial visit, the patient meets the MDC staff including nurses, social workers, and the intake team. All data are reviewed and the MDC team establishes a coordinated care plan. If necessary, advanced imaging such as functional magnetic resonance imaging (MRI) or diffusion tensor imaging is performed to aid in preparations for surgery (**See Figure 1**). Further neuropsychological evaluation may be necessary for some low-grade gliomas or those in or near speech and language areas. Intraoperatively, neurophysiological monitoring

Figure 1. (A) The red arrow points to a small low-grade glioma in the medulla of the brainstem.
(B) DTi was used to show that the descending fibers do not traverse the lesion, but rather are displaced (yellow arrow) by the lesion.

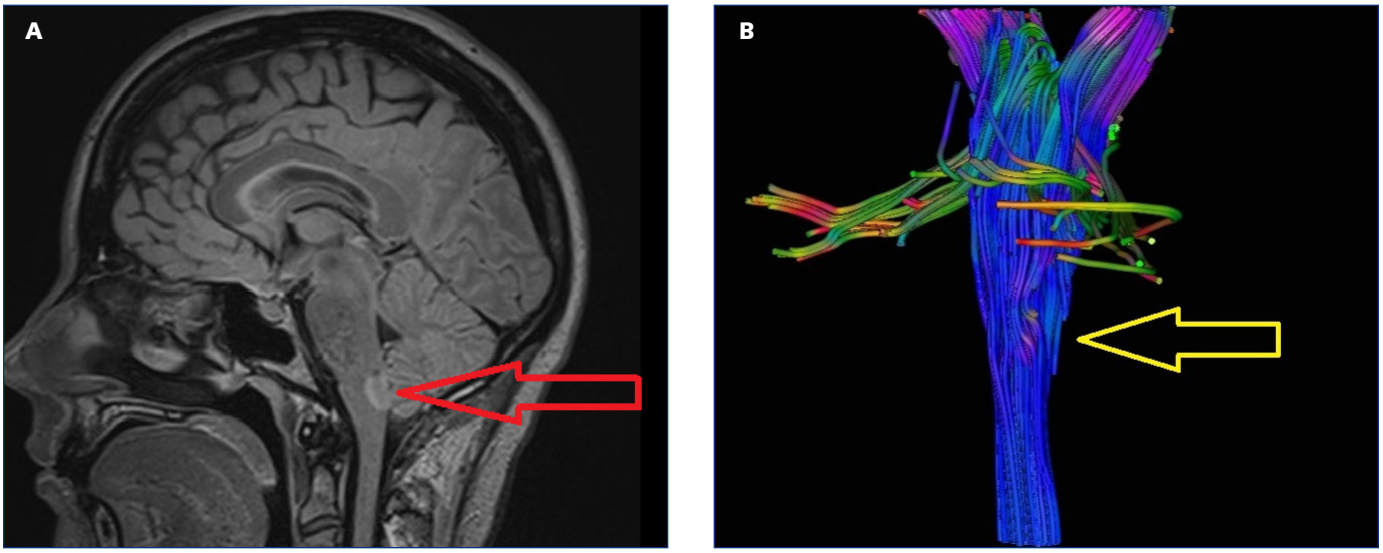
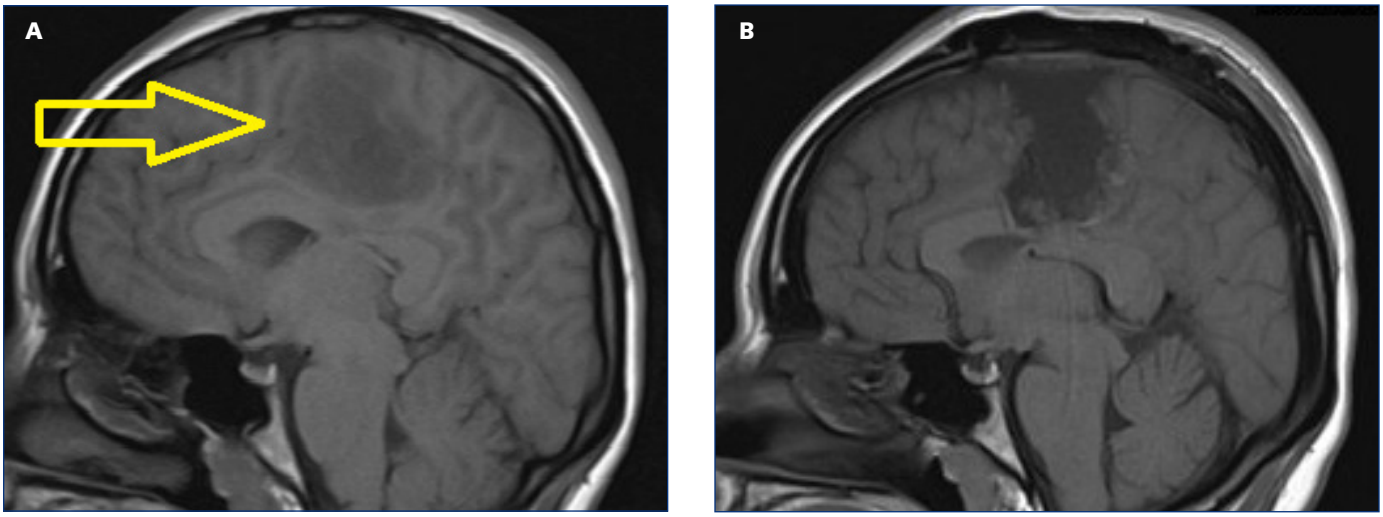


Figure 2. (A) The yellow arrow illustrates a low-grade glioma in the cingulum underlying the motor cortex.
(B) Using neurophysiological techniques including motor evoked potential and subcortical fiber tract stimulation, the lesion was successfully removed.



is undertaken to map out motor and sensory areas (**See Figure 2**) or nearby cranial nerve nuclei. If the lesion is near language areas, an awake craniotomy with speech mapping may be required to achieve maximal safe resection while minimizing the risk of language deficits.

After biopsy or resection, the tissue is studied by a dedicated neuropathologist for both histopathology and molecular markers. A detailed description of the molecular pathology of glioma is beyond the scope of this manuscript. Postoperative MRI is reviewed for completeness of resection and a care plan is formulated by the team. This care plan may include radiation therapy, chemotherapy, tumor treating fields, or clinical trials. Further discussion with the family is begun to deliver the diagnosis and care plan, as well as to engage the patient and family with resources such as local and virtual brain tumor support groups to aid in the social support network for these patients.

Follow-up routinely is weekly during radiation therapy, monthly during active chemotherapy and every three months for high-grade gliomas. Routine surveillance scanning is often used to identify progression of the disease and allow for more timely intervention upon therapeutic failure.

LANDMARKS IN THE CARE OF GLIOMA

For both low-grade glioma as well as glioblastoma, survival is dependent upon age, the patient Karnofsky Performance Score, as well as a host of histopathological and molecular pathological factors. The most important factor in the control of clinicians, is, of course, the percentage of tumor

which can be surgically resected[13,14]. It has been clearly demonstrated that for all types of glioma, the improvement in patient outcomes achieved by the cytoreduction of tumor cells gained is nonlinear and that maximum benefit to the patient is achieved when all tumor which can be removed up to the point of causing a postoperative neurological deficit is beneficial for the patient.

The most important clinical advances in glioma therapy have occurred within the past 15 years. The molecular biology of gliomas involves a host of genetic and epigenetic alterations which are of prognostic importance to tumor classification as well as patient survival. For low-grade gliomas, the most important of the diagnostic and prognostic markers are those of gene rearrangement studies, which suggest the classical oligodendroglioma phenotype and predict responsiveness to chemotherapy, that of chromosome 1p and 19q allelic loss[15]. Loss of 1p/19q alleles predict both sensitivity to chemotherapeutic agents as well as a prognosis which is nearly double that of low-grade gliomas without this genomic loss.

In GBM, attempts have been made to characterize multiple molecular phenotypes, but the single gene with the most prognostic value is IDH1[16]. Mutations in IDH1 are classically identified in GBMs arising from lower-grade gliomas (previously commonly called secondary GBMs to distinguish them from those presenting as *de novo* GBM and often having mutations in the epidermal growth factor receptor) and are associated with improved prognosis. The other commonly cited prognostic factor in GBM is the epigenetic alteration of methylation of the methyl guanine methyl transferase (MGMT) gene promoter[17]. The MGMT methylation at the promoter reduces the expression of the MGMT gene, needed to repair the damage caused by the chemotherapy temozolomide. Thus, patients with methylated MGMT promoter are more susceptible to the effects of the chemotherapeutic temozolomide and are in a better prognostic category.

Prognosis for GBM patients has been among the worst of all malignancies until recently. Survival was less than 12 months as recently as 20 years ago, and progress has been slow. The work of Roger Stupp, who showed that concurrent temozolomide along with radiation therapy improved prognosis over sequential radiotherapy followed by temozolomide marked the first major advance in glioblastoma survival (to 14.6 months) since the advent of radiotherapy and the introduction of nitrosoureas in the 1970s and 1980s[7]. More recently, a series of novel devices, drug therapies and immune strategies have begun to improve survival beyond this mark.

NOVEL THERAPEUTIC ADVANCES

The most recent therapeutic advance to be approved for clinical use in glioma is that of a novel antimitotic therapy called tumor treating fields (TTFs). TTFs are an antimitotic therapy consisting of an alternating electrical current of 100 – 300 kHz delivered via transducer arrays placed on the scalp. In both recurrent and newly diagnosed GBM, TTFs delivered for at least 18 hours per day have been shown to improve survival[7]. In newly diagnosed GBM, the addition of TTFs to radiation and temozolomide improved survival to 24.3 months in treated patients versus 20.4 in the control group. One might note that even the control group with radiation and temozolomide were surviving longer than those from a decade ago.

A host of other small molecule inhibitors and novel drug delivery systems such as convection enhanced delivery have been tried in the past several decades but have failed to show meaningful improvements in survival of GBM. More recently, techniques such as immunomodulatory molecules, such as the PD-1 and CTLA-4 inhibitors have shown improvements in survival of melanoma, lung and renal cell carcinoma and are in trials for GBMs[18].

In addition to immune checkpoint inhibitors, other immune strategies such as peptide vaccines, dendritic cell vaccines[19], and Chimeric Antigen Receptor T-cell (CAR T-Cell) strategies[20] have shown early promise in improving survival for patients with glioma. These topics will be reviewed in another manuscript in this issue.

THE ROLE OF RESEARCH IN GLIOMA – INSIGHTS FROM OUR LABORATORY

Despite many decades of work and recent advances, glioma remains a fatal disease. Thus, no development of a comprehensive brain tumor program would be complete without a research effort. This includes clinical trials with industry and large cooperative groups, but some of the most exciting prospects for improvements in glioma therapy lie within the laboratory. It is the goal of our group to bring several of these to clinical trial within the next several years. With this in mind, we will preview two fields of investigation, glioma migration and micro ribonucleic acid (miRNA) of glioblastoma stem cells.

One of the most vexing aspects of gliomas is that they migrate away from the solid tumor and diffusely infiltrate well beyond apparent margins on MRI. Thus, for anything other than compact, Grade I (benign) gliomas, surgery alone will never be curative. Therefore, we have studied within our laboratory how glioblastoma cells interact with the brain environment to migrate as well as how we might manipulate these pathways to aid in therapy. We are manipulating these pathways to promote the return of remaining cancer cells to the resection site by placing a pro-migratory protein (LCN2) in a slow release hydrogel placed within the resection cavity to hopefully improve the results of radiation therapy. In addition, we have found a small molecule inhibitor of a tyrosine kinase (Lck), which enables pseudopodia extension and migration in GBM stem cells. We feel that manipulation of the "On" and "Off" pathways for migration can be used to

improve patient outcomes and expect to begin clinical trials after we complete our small animal model data.

In addition, our laboratory is investigating the role of miRNA – the regulators of RNA transcription – to identify how regulation of these small switches controls the ability of cancer cells to self renew and replicate in GBM stem cells. Thus far, we have narrowed the control of this crucial feature of cancer – the ability of cells to remain stem-like and resist therapy – to 9 likely miRNA candidates. Our preliminary work suggests that miRNA-mediated control of RNA methylation may be the molecular switch that changes GBM stem cells to the cancer cells we typically associate with GBM. We hope that this signature may yield prognostic data and reveal pathways for therapeutic intervention.

Of course, none of this has much meaning without educating the future generation of oncologists and neurosurgeons to care for patients with glioma. We anticipate beginning advanced training of neurosurgical oncology fellows within the year. Once this is complete, the comprehensive brain tumor center will close the circle from the patient, to the student, to the laboratory, and back, to be able to provide the best care for patients afflicted with glioma.

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