Primary brain tumors are defined as any intracranial tumor involving the brain parenchyma or surrounding structures such as the meninges, the pituitary or the pineal gland. According to the 2007-2008 Central Brain Tumor Registry of the United States statistical report (reflecting data from 2000–2004), approximately 51,410 new cases of primary brain and central nervous tumors were expected to be diagnosed in the United States in the year 2007, of which 20,500 were expected to be malignant. Gliomas, tumors arising from glial cells (astrocytes, oligodendrocytes and ependyma) comprise approximately 36 percent of all primary brain tumors. The resulting tumors are known as astrocytomas, oligodendrogliomas and ependymomas respectively. Of these, astrocytomas and glioblastoma multiforme (grade IV astrocytoma) make up 75 percent of all gliomas. Glioblastoma multiforme (GBM) itself comprises approximately 51 percent of all gliomas.

Astrocytomas are graded according to a histological paradigm that correlates closely with aggressiveness and prognosis. There are a variety of three and four-tiered grading schemes. The most commonly used grading schemes utilize a four-tiered system:

Grade 1 astrocytomas are reserved for low-grade, and potentially surgically curable, childhood tumors such as pilocytic astrocytoma.

Grade 2 (low-grade) astrocytomas consist of a diffuse tumor, intermingling with normal brain tissue. On pathologic examination, there is increased cellularity, nuclear pleomorphism, and rare, if any, mitoses. There is no vascular hyperplasia or necrosis. These tumors tend not to enhance on post-contrast MRI.

Grade 3 (anaplastic) astrocytomas consist of a tumor that may be diffusely infiltrating or may be solid but usually with components of both. These tumors have increased cellularity, nuclear pleomorphism, mitoses, and may (based on the specific grading criteria) have some degree of vascular hyperplasia. No necrosis is present.

Grade 4 astrocytoma (glioblastoma multiforme) is a tumor that is solid, often with a necrotic center and a viable periphery. Glioblastomas invariably infiltrate the surrounding brain parenchyma, making gross total resection of these tumors impossible. Pathologically, there is increased cellularity, nuclear pleomorphism, mitoses, vascular hyperplasia, and necrosis.

GBM may be diagnosed at any age, though the peak incidence is between ages 55 and 74. GBM is 50 percent more common in men than in women. Risk factors for development of GBM include previous exposure to ionized radiation as well as genetic predisposition (neurofibromatosis types I and II, tuberous sclerosis, Turcot syndrome, and Li Fraumeni syndrome). Employment in synthetic rubber manufacturing, petroleum refining or production work, and exposure to vinyl chloride or pesticides have also been associated with GBM. A recently published meta-analysis has suggested an association between cell phone use and increased risk of glioma and acoustic neuroma.

GBM may arise either as a primary tumor (de novo GBM) or may develop from pre-existing lower grade astrocytomas (secondary GBM). These tumor types differ genetically; the loss of PTEN and EGF receptor amplification are seen in de novo GBM, whereas genetic alterations typical in lower grade astrocytomas (abnormalities of p53, PDGF receptor alpha and p16) are seen in secondary GBMs. The differences in genotype resulting in distinct phenotypic expression may have implications for treatment utilizing targeted therapies.

Approach to the Acute Patient
Most commonly, patients will present with progressive neurological symptoms, such as headache, focal weakness, change in mental status, aphasia, or gait disturbances. Seizures have been reported to occur as the initial symptom in 30-60 percent of patients.

Patients presenting with symptoms and signs indicative of central nervous system pathology typically undergo imaging of the brain. Computerized tomography (CT) scanning typically reveals a hypodense lesion with mass effect and midline shift.
Following administration of IV contrast, a portion of the hypo-
dense area may enhance. All patients with a suspected brain
tumor should undergo contrast-enhanced magnetic resonance
imaging (MRI). GBM appears as isointense to hypointense
nodules with diffuse or irregular enhancement, often in a ring-
like pattern, after contrast administration on T1-weighted
images, while they are hyperintense in both T2 weighted and
fluid attenuation inversion recovery (FLAIR) sequences.
Additional T2/FLAIR hyperintensity and T1 hypointesity is
seen around the enhancing portion of the tumor, representing
vasogenic edema and infiltrative tumor.

Corticosteroids such as dexamethasone are used to treat neu-
rological deficits. Surgery should be the first therapeutic modal-
ity for GBM. When feasible, a gross total resection should be
performed. Complete resection, however, is rarely if ever
achieved given the infiltrative nature of these tumors. Maximal
surgical resection allows for the palliation of neurological symp-
toms and improvement in quality of life. Additionally, there is
evidence that gross total resection prolongs survival but not dis-
ease-free survival.6

Patients presenting with seizures should be placed on anti-
epileptic medication (AED) at the time of presentation. AEDs
are used prophylactically during surgery but should be stopped
after surgery in patients who have not had a seizure, as there is
no evidence that use of AEDs prevents seizures. Non-hepatic
enzyme inducing AEDs are typically utilized when a patient
requires chronic seizure prophylaxis. A number of chemother-
apapeutic medications (such as Irinotecan) and newer targeted
therapies (particularly tyrosine kinase inhibitors) undergo
hepatic metabolism and thus may be rendered ineffective in the
setting of hepatic enzyme induction.

If gross total resection is not feasible, maximal debulking
should be achieved to alleviate neurological symptoms and to
obtain an optimal pathology specimen. Stereotactic biopsy may
be performed for tumors in eloquent regions; however, tumor
grading may be underestimated.

Treatment
Treatment of GBM consists of combined radiation therapy
(RT) and chemotherapy. A six week course of approximately
6000 centigray (cGy) of external beam RT in 30 daily fractions
is provided to the entire abnormality (enhancing tumor plus
T2/FLAIR abnormality) and a surrounding margin of approxi-
mately 2cm. Temozolomide (TMZ), an oral alkylating agent, is
provided on a daily basis during radiation therapy at a dose of
75mg per square meter of body surface area (mg/m²). Follow-
ing the completion of RT, temozolomide is stopped for
four weeks and is then resumed at a dose of 150–200mg/m² for
five consecutive days out of every 28 for a minimum of six
months. During radiation therapy, prophylaxis against pneumo-
cystis carinii pneumonia is provided in the form of trimetho-
prim/sulfamethoxazole, dapsone, atovaquone, or inhaled pen-
tamidine.7

The addition of temozolomide to radiation therapy improves
both progression-free survival and overall survival compared with
radiation therapy alone. A phase III trial performed by the
European Organisation for Research and Treatment of Cancer
(EORTC) and the National Cancer Institute of Canada (NCIC)
randomized patients to standard radiotherapy (6000 cGy in 30
daily fractions of 200 cGy) with or without concurrent TMZ at a
dose of 75mg/m²/day. Patients receiving chemotherapy with
radiation also received six months of adjuvant TMZ at a dose of
150 to 200mg/m² daily for five days every 28 days. Median sur-
ival improved from 12.1 to 14.6 months, median progression
free survival improved from 5.0 months to 6.9 months, and two-
year survival from 10.4 percent to 26.5 percent.8

A translational research study performed in conjunction
with this trial measured the impact of DNA repair mecha-
nisms on outcome. O6-methylguanine DNA-methyltrans-
ferase (MGMT) is an excision repair enzyme that has been
associated with resistance to chemotherapy in a variety of
tumors, because it may reverse the damage to DNA rendered
by alkylating agents by removing alkyl groups from the O6
position of guanine. The presence or absence of MGMT can
be determined by the absence or presence, respectively, of a
methylated MGMT gene promoter. Approximately 45 per-
cent of all tumors analyzed had methylated promoter. Patients
with methylated MGMT promoter treated with TMZ/RT
had a median survival of 22 months and a two-year survival
rate of 46 percent. This is in contrast to those treated with ini-
tial RT alone, who had a median survival time of 15 months
and a two-year survival rate of 23 percent. Patients with an
unmethylated promoter treated with TMZ/RT had a median
survival time of 13 months and a two-year survival rate of 14
percent, and those treated with RT only had a median survival
time of 12 months and a two-year survival rate of less than
two percent.9

BCNU-impregnated biodegradable wafers (Gliadel®) are
FDA-approved for use at the time of initial surgery in patients
with malignant glioma (GBM and anaplastic astrocytoma/oligo-
dendroglioma). A phase III trial comparing Gliadel versus place-
bo wafers in patients with newly diagnosed malignant gliomas
showed prolonged survival. However, subset analysis of patients
with glioblastoma indicated that while there is a survival advan-
tage for patients with GBM (13.1 months versus 11.4 months),
this difference was not statistically significant.9

Other than the concurrent use of temozolomide and radia-
tion therapy, no other form of treatment has been shown to be
more effective than radiation therapy alone. This includes dose
escalation of radiation therapy beyond 6000 cGy, as well as the
use of other forms of chemotherapy either during or after radiation therapy.\textsuperscript{4,10}

**Treatment at Recurrence**

GBMs invariably recur. Typically, patients are monitoring utilizing neuroanatomical imaging (preferably MRI) on a routine basis following the completion of initial radiation therapy and chemotherapy. The first study is typically performed approximately four weeks after the completion of radiation therapy and subsequent studies are performed every two to three months. Imaging is also indicated for changes in neurological status, such as the onset of new neurological symptoms or recurrent seizures. Tumors may also expand in the setting of radiation necrosis, which may occur several months after completion of radiation therapy. If there is doubt as to whether tumor expansion represents recurrence or necrosis, functional imaging, such as with PET scan, perfusion MRI (measuring regional cerebral blood volume), or MR spectroscopy, can be performed. However, surgical debulking is frequently required. Surgery will palliate neurological symptoms and will aid in differentiating necrosis from viable tumor.\textsuperscript{4}

If necrosis is suspected, treatment consists of observation and corticosteroids, if needed. Once a recurrence has been identified, a variety of therapeutic options are available. These include:

- Gliadel wafer placement. BCNU wafers have been shown to prolong survival compared with the use of placebo wafer.\textsuperscript{12} This is typically performed at the time of initial tumor resection, once viable tumor has been identified on unfrozen section.
- Stereotactic radiosurgery or fractionated stereotactic radiotherapy boosts.\textsuperscript{13}
- Chemotherapy, including the use of temozolomide (especially if there has been no previous treatment failure), nitrosoureas (carmustine or lomustine), PCV (procarbazine, CCNU [lomustine] and vincristine), procarbazine, or carboplatin. Objective response rates are low, and there is no evidence that chemotherapy for recurrent disease results in prolonged survival.\textsuperscript{4}
- Bevacizumab, a monoclonal antibody, is frequently used for tumor recurrence and is described further below.

Clinical trials investigating new agents are available at many centers throughout North America.

**Targeted Therapies**

A variety of agents targeting specific phenotypic abnormalities are undergoing investigation. Two common targets are intracellular signaling pathways and angiogenesis. Intracellular signaling pathways are ways by which a surface receptor, through a transduction cascade, induces cellular division. These surface receptors may become amplified or abnormal in GBM. Representative receptors include epidermal growth factor receptor (EGFR), platelet-derived growth factor (PDGF), and insulin-like growth factor receptor (IGFR). Inhibitors of the transduction cascade, such as PTEN (phosphatase and tensin homolog) reside on chromosome 10, which is frequently deleted in glioblastoma.\textsuperscript{4}

EGFR is amplified and overexpressed in approximately 50 percent of GBMs. Clinical trials utilizing EGFR tyrosine kinase inhibitors (gefitinib and erlotinib) had revealed activity in a subset of patients, though this activity did not correlate with EGFR overexpression. Other agents have targeted other points in the transduction cascade. This includes the protein kinase C inhibitors, such as enzastaurin, inhibition of activation of the Ras protein utilizing farnesyltransferase inhibitors, and inhibition of the mammalian target of rapamycin (mTOR) utilizing mTOR inhibitors such as temsirolimus and everolimus. Clinical trials have suggested minimal activity of these agents as monotherapy. Because of the redundancy of the transduction cascade, it is likely that multiple agents will be needed to provide clinical benefit.\textsuperscript{4}

Growth and infiltration of GBM requires endothelial cell proliferation and neovascularization. This is regulated by proangiogenic cytokines, including vascular endothelial growth factor (VEGF) and integrins. Bevacizumab is a recombinant human-
ized monoclonal antibody that directly binds VEGF, preventing its interaction with the endothelial cell VEGF receptor (VEGFR). Bevacizumab is currently FDA-approved for use in metastatic colon cancer, breast cancer, and non-squamous nonsmall cell lung cancer. Its use, in combination with chemotherapy, such as irinotecan, has resulted in an approximately 60 percent objective response rate. While there have been no comparative clinical trials indicating a progression-free and overall survival benefit, the reported six-month progression free survival in patients with recurrent disease is 30 percent and the reported median survival was approximately nine months in a phase II study. Figure 1 shows the objective response to bevacizumab and temozolomide in a patient with a recurrent glioblastoma. A significant reduction in both enhancing tumor and in flair abnormality was seen after three treatments, each provided two weeks apart. This patient was not on corticosteroids, and a left hemiparesis resolved in the six-week interval between MRIs. While not FDA-approved for use in glioblastoma, the use of bevacizumab either as monotherapy or in combination with other forms of chemotherapy has become first line treatment for recurrent glioblastoma.

The VEGF receptor can also serve as a target for anti-angiogenic therapy. A variety of orally-administered small molecules, such as sunitinib, sorafenib, cediranib and vatalanib, are currently in clinical trials. Cediranib has shown objective radiographic responses similar to that seen with bevacizumab. Investigations into the mechanism of action of cediranib have suggested that VEGF receptor inhibition leads to normalization of tumor vasculature and restoration of the blood-brain barrier, reducing contrast enhancement and edema. This effect has been observed with anti-VEGF therapy in colorectal cancer with responses attributed to normalization of the vasculature, decreased interstitial pressure, and better oxygenation and drug delivery.

Integrins are cell surface receptors mediating interaction with the extracellular matrix, regulating cell adhesion and migration. During angiogenesis, integrins are essential for endothelial cell migration, proliferation, and survival. Inhibitors of integrin have been shown in animal models to inhibit angiogenesis with resulting inhibition of tumor progression. Cilengitide, which binds to the αvβ3 and αvβ5 integrin receptors, has shown evidence of activity as a single agent in a phase II study.

Immunotherapy

Immunotherapy or “vaccine” therapy involves the induction of an immune response against an individual tumor. Typically, the immune stimulant is a patient’s own tumor. The tumor is processed in a variety of ways, depending on the clinical trial, and is presented back to the immune system, usually by subcutaneous presentation. Immunotherapy has shown promise, with responses and increase survival described in a number of clinical trials.

Conclusions

Glioblastoma multiforme is the most common and most aggressive type of glioma. Current treatment utilizing a combination of chemotherapy and radiation therapy modestly improves survival and progression-free survival. There are, however, a variety of molecular mechanisms differentiating glioblastoma, such as the presence or action and absence of GMT, as well as other phenotypic abnormalities, that can be exploited to derive additional treatment benefit and for which investigations are ongoing. Ultimately, it is hoped that treatment will become individualized, such that a treatment plan will be designed based on an individual patient’s tumor phenotype.

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