CLINICAL PICTURE:
A 60 years old male patient presented clinically with rapidly progressive left sided hemiplegia and manifestations of increased intracranial tension. (To inspect the patient's full radiological study, click on the attachment icon (The paper clip icon in the left pane) of the acrobat reader then double click on the attached file) (Click here to download the attached file).

RADIOLOGICAL FINDINGS:

Figure 1. Precontrast CT scan showing diffuse hypodensities involving the left thalamic area, left internal capsule and left basal ganglionic area. The hypodensities, most probably, represent tumor tissues, peritumoral edema and reactive astrogliosis.
Figure 2. Postcontrast CT scan images showing a densely enhanced space occupying lesion involving the left thalamic area with positive mass effect and peritumoral edema involving the white matter and sparing the gray matter (vasogenic edema). Notice the peritumoral satellitosis (B).

CT guided stereotactic biopsy revealed Mixed astrocytoma (Grade III-Grade IV diffuse astrocytoma). The patient was not operated upon, he received radiotherapy only to die 4 month following clinical diagnosis.

Common pathological characteristics of diffuse astrocytomas

- Diffuse astrocytomas are tumors predominantly composed of astrocytes. Unless otherwise indicated, the term usually applies to diffusely infiltrating neoplasms (WHO grades II through IV).

- Diffuse astrocytoma is unusual in the first decade of life and most commonly presents in older children or young adults up to the age of 40 to 45.

- All diffuse astrocytomas, particularly the diffusely infiltrating variety, have a tendency toward progression to more malignant forms. Diffuse astrocytomas have a peculiar tendency to change its grade over time into the next higher grade of malignancy and the condition is age dependant. A change in the grade of diffuse astrocytoma is more likely to occur in the older age group.
Primary tumors of the thalamus account for only 1-1.5% of all intracranial tumors and approximately 25% of them arise in children aged 15 years or under. Thalamic gliomas might be unilateral or bilateral. Diffuse and involvement of thalamic nuclei by these tumors makes surgical therapy very difficult and no case of radical removal has been described in the literature. Consequently, the main role of surgery is limited and usually performed for a histological diagnosis. Generally, these gliomas are low-grade astrocytomas (grade II of WHO classification), but limited anaplastic areas may be encountered.

Diffuse astrocytoma often spreads widely through the brain but without destruction and also without interruption of normal function. Microscopically, tumor cells infiltrate between myelinated fibers in a nondestructive manner (perineuronal satellitosis). The local spread of diffuse astrocytomas (forming gliomatosis cerebri and butterfly gliomas) does not mean that the tumour grade is grade IV (glioblastoma multiforme), local spread can occur in grade II and grade III and in the author experience gliomatosis cerebri and butterfly gliomas are much more commonly seen in grade II astrocytomas and has not been encountered in grade III (anaplastic astrocytomas) and grade IV (glioblastoma multiforme). It takes a long time for a diffuse astrocytoma to cross the corpus callosum to the opposite hemisphere to form a butterfly glioma. Patients harbouring glioblastomas have a much shorter life span for their tumours to form butterfly gliomas, however cases were reported for glioblastomas forming butterfly tumours.

These glioma cells migrate through the normal parenchyma, collect just below the pial margin (subpial spread), surround neurons and vessels (perineuronal and perivascular satellitosis), and migrate through the white matter tracks (intrafacicular spread). This invasive behavior of the individual cells may correspond to the neoplastic cell's reacquisition of primitive migratory behavior during central nervous system development. The ultimate result of this behavior is the spread of individual tumor cells diffusely over long distances and into regions of brain essential for survival of the patient. The extreme example of this behavior is a condition referred to as gliomatosis cerebri, in which the entire brain is diffusely infiltrated by neoplastic cells with minimal or no central focal area of tumor per se. Furthermore, 25% of patients with GBM have multiple or multicentric GBMs at autopsy. Although GBMs can be visualized on MRI scans as mass lesions that enhance with contrast, the neoplastic cells extend far beyond the area of enhancement.

In practice considerable histological heterogeneity in astrocytic tumours is found (i.e., low grade areas with Rosenthal fibers and calcification can be intermixed with with frankly malignant ones).

The differences in histologic features, potential for invasiveness, and extent of progression likely reflect genetic differences acquired during astrocytoma growth.

Grade IV astrocytomas (glioblastoma multiforme) differ from diffuse astrocytoma grade II and grade III (anaplastic astrocytomas) in the presence of gross necrosis, and microscopically in the presence of vascular endothelial hyperplasia and tumour hemorrhage.

Primary tumors of the thalamus account for only 1-1.5% of all intracranial tumors and approximately 25% of them arise in children aged 15 years or under. Thalamic gliomas might be unilateral or bilateral.

Diffuse and involvement of thalamic nuclei by these tumors makes surgical therapy very difficult and no case of radical removal has been described in the literature. Consequently, the main role of surgery is limited and usually performed for a histological diagnosis. Generally, these gliomas are low-grade astrocytomas (grade II of WHO classification), but limited anaplastic areas may be encountered.

Radiotherapy and chemotherapy are sometimes utilized as adjuvant therapy, but their role is questionable. Outcome is generally poor, independently of the therapy that is utilized. Rapid fatal evolution after diagnosis and the almost complete unresponsiveness of these tumors to radiotherapy make these rare tumors difficult to treat. Anaplastic gliomas usually show enhancement after contrast administration.

Severe dementia and personality modification observed in adults affected by bilateral thalamic glioma is attributed to the involvement of dorsomedial nuclei of thalami and their connections with temporal and frontal lobes [9]. Bilateral thalamic glial tumors are rare and less than 50 cases have been published in the literature [1-8].

**DIAGNOSIS:**

**THALAMIC GLIOMA**
The past of glioblastoma multiforme

The most common cancer arising from the brain is the glioblastoma multiforme (GBM). It is also the most deadly, [1] representing the most aggressive subtype among the gliomas, a collection of tumors including astrocytomas and oligodendrogliomas (see Table 1). In 1926, Bailey and Cushing, in describing spongioblastoma multiforme, the label then used for GBM, noted that:

- It is from this group doubtless that the generally unfavorable impression regarding gliomas as a whole has been gained. It is not only the largest single group in the series but at the same time is one of the most malignant. In the five unoperated cases, the average duration of life from the onset of symptoms was only three months, which speaks well on the whole for the average survival period of twelve months for those surgically treated. [2]

Since their seminal work, the median survival of 12 months has not changed markedly. Both data from the 1960s and current data [4] confirm that the extent of surgical resection is an important prognostic factor. However, as Bailey and Cushing observed, GBMs have – infiltrating propensities, and when enucleation is attempted, the growth is found at the depth to spread into and merge with the normal cerebral tissue without recognizable demarcation. [2] In prior eras, radical surgical excisions, including removal of the entire cerebral hemisphere containing the tumor, [5] were occasionally attempted, yet patients who survived the hemispherectomy died of recurrent tumor, [6] clinically proving the importance of the histologic observation that tumor cells invade throughout the brain. In the modern age, brain imaging may disclose macroscopic tumor in the opposite hemisphere (see Figure 1) or even gliomatosis cerebri literally a brain full of tumor. In the years leading to up to World War II, the German pathologist Scherer, whose scientific discoveries were tainted by his Nazi activities, [7] described secondary structures [8,9] that further characterized invasive tumor cells. These structures are secondary because they are dependent for their formation on underlying normal brain structures, as opposed to primary structures of the tumor such as pseudopalisading necrosis and microvascular proliferation. Examples include perineuronal and perivascular satellitosis (accumulation of tumor cells around neurons and blood vessels), subpial spread, and infrafascicular tracking such as infiltration along corpus callosum and other white matter tracks (see Figure 2).

Advances in surgical technique, imaging, and targeting of radiotherapy (RT) are important contributions to local control. However, changing GBM from a disease that kills quickly to one that can be managed as a chronic illness, such as hypertension or diabetes mellitus, will require systemic therapies targeting tumor cells infiltrating throughout the brain, such as chemotherapy, immunotherapy, and small molecule pathway inhibitors.

The current status of glioblastoma multiforme

Currently, treatment for GBM involves both local and systemic therapy. Surgery and partial brain RT are the standard locally directed therapies. Some physicians also advise intra-operative placement of chemotherapy containing polymers (i.e. Gliadel wafers) directly into the surgical bed in an attempt to prolong local control. [10] While there is a modest survival benefit, the use of these polymers remains controversial because of the potential for toxicity. Other treatment modalities that target disease localized to the surgical bed or the surrounding area have included brachythrapy and stereoelectric radiosurgery (with either a linear accelerator or gammaknife), neither of which are commonly advised. Convection-based chemotherapies delivered by catheter infusion, such as local delivery of pseudomonas exotoxin linked to either interleukin [13] (IL-13) or transforming growth factor-a (TGFa), [11] are available in clinical trials for some patients. These trials take advantage of differences in the expression of proteins (such as growth factor receptors) on the surface of residual tumor cells in the periphery of the operative bed to deliver the toxin to tumor cells, but spare normal brain.

By contrast, systemic chemotherapy targets tumor cells beyond the reach of local therapies. The most commonly prescribed systemic chemotherapy for GBM is temozolomide (Temodar®), an alkylator that became available during the last decade. The effectiveness of temozolomide in the management of GBM at diagnosis was recently demonstrated by a large multinational study. [4] A modest survival benefit of 2.5 months for concurrent temozolomide with RT (14.6 months median survival) was observed relative to RT alone (12.1 months median survival). [4] In addition, while the survival benefit was still
present two years after diagnosis, only 10.7% of patients were progression-free and only 26.5% of patients were alive at that point. [4] While systemic chemotherapy improves the outcome for some patients, long-term disease control therefore remains elusive.

Table 1. Common Gliomas. The gliomas are assigned a grade by the World Health Organization (WHO) depending on histologic features that predict behavior. This classification scheme is derived from the clinicopathologic studies of Bailey and Cushing.2 Grade I tumors, such as juvenile pilocytic astrocytomas, are generally focal rather than diffuse and are potentially curable by surgical excision. WHO grade II–IV tumors are diffusely infiltrative. WHO grade III–IV tumors are termed ‘high grade’ or malignant. GBMs, or grade IV astrocytomas, are the most aggressive subtype.

<table>
<thead>
<tr>
<th>WHO grade</th>
<th>Astrocytic Tumor</th>
<th>Oligodendrocytic Tumor</th>
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<td>II</td>
<td>Astrocytoma</td>
<td>Oligodendroglioma</td>
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<tr>
<td>III</td>
<td>Anaplastic Astrocytoma</td>
<td>Anaplastic Oligodendroglioma</td>
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<tr>
<td>IV</td>
<td>Glioblastoma Multiforme</td>
<td>Not applicable</td>
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Discoveries during the last several years have improved the understanding of glioma and general cancer biology markedly. Generally, a cancer comprises cells that either divide or survive when they should instead undergo either cell cycle arrest or die. These abnormalities are also not mutually exclusive, and most cancers, including GBMs, are driven by several molecular abnormalities. The signal to divide is typically provided by a growth factor (ligand). Examples include TGF?, epidermal growth factor (EGF), platelet-derived growth factor (PDGF), and vascular endothelial growth factor (VEGF). Such ligands interact with cells through receptors including EGF receptors (EGFRs), PDGF receptors (PDGFRs), and VEGF receptors (VEGFRs). Receptor activity is linked with cellular processes such as mitosis or invasion by signal transduction cascades. Examples of signal transduction cascades important in human GBMs include those activated by the oncogenes Ras, Akt, and Src. [12] In cancer cells, these pathways are disrupted through several mechanisms. For example, EGFR is overexpressed in up to 92% of astrocytomas, [13] and up to 62% of GBMs express EGFRvIII, [14] a mutant receptor that is active independently of ligand. Co-expression of EGF and EGFR is in GBMs leads to a potential autocrine loop. An analogous loop is created by PDGF and PDGFR co-expression in up to 94% of high-grade oligodendrogliomas. [17–19] Regardless of ligand or receptor status, close to 100% of GBMs exhibit activation of Ras, and approximately 70% exhibit activated Akt. [21,22] the latter typically through loss of the tumor suppressor gene phosphatase tensin homolog on chromosome ten (PTEN), [23–25] which normally represses Akt activation. Src is detected in 67% of GBMs.26 Finally, control over cell division is normally maintained by tumor suppressors, such as an inhibitor of CDK4A (INK4A) and its alternative reading frame (ARF), as well as p53, which also contributes to DNA repair and apoptosis, and other enzymes. Disruptions of normal cell cycle control of one form or another have been observed in almost all GBMs. [12,27]

Moreover, the modeling of gliomas in mice has demonstrated that abnormalities of ligands, receptors, signal transducers, and proliferation cause gliomas. For example, combined activation of Ras with Akt in glial progenitors is sufficient to induce GBMs in mice, [22] and transgenic expression of activated forms of Ras [28] or Src [29] in glia leads to GBMs following spontaneous development of cooperative oncogenic abnormalities. Modeling has also demonstrated that PTEN loss is functionally equivalent to Akt activation, [30] when combined with activated Ras. PDGF overexpression in glia causes high-grade oligodendrogliomas [31,32] that also exhibit pathologic features of GBMs, including pseudopalisading necrosis and microvascular proliferation. The threshold to tumor formation is lowered by disruption of Ink4a-Arf or p53 expression. [31,33,34]

While more is learned about glioma biology, small molecule inhibitors are being developed that target the causal pathways. [35] For example, several inhibitors of EGFRs are under investigation in clinical trials. These include the EGFR inhibitors erlotinib (OSI-774/Tarceva), gefitinib (ZD-1839/Iressa), and lapatinib (GW572016). The PDGFR inhibitors imatinib (STI-571/Gleevec) and PTK787, both of which have other targets, are also in use. Signal transduction cascade blockers are also
being studied. One example is R11577, which targets the enzyme that activates Ras. Rapamycin (sirolimus), CCI-779 (temsirolimus), and Rad-001 (everolimus) target mTOR, one of the key enzymes activated by Akt.

Figure 2. Histology of Gliomas. (A) Pseudopalisading (arrow) necrosis (arrow head) and (B) microvascular proliferation (arrow) are the classic histologic findings in glioblastoma multiforme (GBM). Secondary Scherer structures (C) involve tumor cells (arrow heads) accumulating around blood vessels (BV, long arrow), and neurons (N, long arrow) in a low grade (WHO grade II) oligodendroglioma. Such perivascular and perineuronal satellitosis, along with intrafascicular growth and subpial accumulation (not shown), contribute to the diffusely infiltrative nature of gliomas throughout normal brain structures. (Click to enlarge figure)

Unfortunately, despite initial enthusiasm, treatment of GBMs as well as systemic malignancies with these small molecule inhibitors as single agents has generally been disappointing. For example, published interim and final reports of trials involving gefitinib, [36,37] erlotinib, [38–40] imatinib, [41,42] PTK787, [43,44] and CCI-779[45] monotherapy for recurrent high-grade gliomas have not shown response or survival rates that are markedly superior to those observed with traditional chemotherapies, such as temozolomide [4,46–48] or carmustine (BCNU). [49] However, there are individual patients treated with these agents who experience durable objective responses or sustained stable disease. Therefore, these agents are likely to have a role in GBM management.

Figure 3. Pathways Important in GBM Biology. An extracellular ligand such as EGF,TGFα, or PDGF induces dimerization of receptors such as EGFR or PDGFR. Receptor stimulation activates intrinsic tyrosine kinase (TK) activity and EGFR and PDGFR are therefore called receptor tyrosine kinases (RTKs). RTKs then activate the Akt, Src, and Ras signal transduction cascades. Tumor cell growth is driven by ligand or receptor overexpression, constitutively activating receptor mutations (e.g. EGFVIII), or signal transduction activity. Pointed (green) and block (red) arrows indicate pathway activation and inhibition, respectively. The inhibitors shown and others are under investigation in the treatment of GBMs.

Future perspective of glioblastoma multiforme

In addition to surgical resection and RT, the future of GBM therapy is likely to involve both additional measures to improve local control (such as convection or catheter delivery of antitumor agents into the operative cavity) and systemic treatment to address infiltrative disease distant from the main tumor bed. However, a major thrust of research will be tissue analyses looking for molecular features that predict sensitivity of GBMs to either traditional chemotherapies or small molecule inhibitors. Tailoring therapy with specific drugs to those patients is most likely to improve response rates and spare patients who are unlikely to benefit the expense and potential toxicity of these agents. Determination of a molecularly effective dose (MED) (inhibits a pathway), may also be more useful than the traditionally used maximally tolerated dose (MTD).

An example of a molecular prognostic factor is loss of heterozygosity for chromosomes 1p and 19q in anaplastic oligodendrogliomas, which predicts both sensitivity to chemotherapy and radiation, as well as longer overall survival. [50] Consequently, some neurooncologists are currently using results of 1p/19q analysis to guide therapy, [51] although this remains an area of controversy. Other genomic alterations are also predictive—PTEN loss is associated with poor survival for patients with anaplastic oligodendrogliomas [52] and is likely to predict poor outcome from GBM. [23,53,54] More recently it was reported that GBMs, in which O6-methylguanine- DNA methyltransferase (MGMT) expression was silenced by gene methylation, were more sensitive to temozolomide than tumors with unmethylated MGMT. The likely explanation is that MGMT may counteract temozolomide activity by removing alkyl groups on DNA. [55] It is unclear whether MGMT
methylations impacts sensitivity of other glioma subtypes to temozolomide, yet MGMT methylation status may be used in the near future to guide therapy.

Individualized medicine determined by molecular rather than simply histologic phenotype may also guide therapy with small molecule inhibitors. Somatic mutations in exons 18-21 of EGFR are associated with sensitivity of lung cancer to gefitinib [56-58] or erlotinib. [58] However, the authors and others have not found these mutations in gliomas. [34,57,59,60] Efforts are under way to identify the molecular features that predict sensitivity of GBMs to EGFR and other receptor tyrosine kinase (RTK) inhibitors.

Response and survival rates may also be improved through combination therapy. For example, preliminary data suggest that concurrent therapy with imatinib (PDGFR/VEGFR inhibitor) and hydroxyurea (a more traditional chemotherapy) is more effective than imatinib monotherapy. A small series with 14 evaluable patients with recurrent GBMs demonstrated a disease control rate (complete response or partial response or stable disease) of 64% for patients treated with this combination. [61] By contrast, imatinib monotherapy led to a disease control rate of 29%. [42] Larger trials of this and other combinations, such as temozolomide with PTK787, are under way. (Click here to download master degree thesis "Non surgical management of brain tumors" in PDF format)

SUMMARY

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, [63] 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 is 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). [64] 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 timepoint was quite small. [65]

Perhaps the most significant advance in the management of glioblastomas emanates from the work of Stupp et al. [65] 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, highgrade GBM undergoing resection with BCNU wafer insertion followed by the combination of radiotherapy plus temozolomide. Early interim data have been presented in abstract form. [67] 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, [87] 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 highgrade 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. [68]

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, multiinstitutional 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 reirradiation 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. [69]

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. [70] 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 endpoint 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) 26051—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. [73] Both studies demonstrated that the addition of PCV improved PFS without impacting on overall survival (OS). Although chromosome 1p/19q loss does predict chemo sensitivity, 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). [74] 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. [75]

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%. [76,77] 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. [78] 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 sixmonth PFS or 12-month survival. [79] Optimal dosing of these oral agents, especially while patients are taking enzyme-inducing anti-
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. [81] 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. Hégi 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. [82] 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. [82] 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. [83] 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). [84] Enzastaurin also appears to be safe in conjunction with radiation therapy and temozolomide in patients with newly diagnosed GBM. [85] GBM is highly angiogenic, and vascular endothelial growth factor (VEGF) is amplified in most GBM tumors. [86] 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. [87] 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. [89,90,91]

**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. [89] 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.

**Addendum**

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