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Neuro-oncology (Neoplasms)

High-Grade Gliomas

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Opinion statement

High-grade gliomas (HGGs) should be treated with maximal, safe surgical resection followed by 57–60 Gy of partial-field external beam or intensity-modulated radiotherapy to a 2 cm margin surrounding the resection cavity. The standard of care for newly diagnosed glioblastoma includes concurrent temozolomide (TMZ) during radiotherapy and adjuvant TMZ for six or more cycles. The optimal role of chemotherapy in anaplastic gliomas is unresolved. Carefully selected patients with anaplastic gliomas can be treated with combination chemotherapy (procarbazine, lomustine, vincristine; PCV) or TMZ as initial therapy after surgical resection, adjuvant therapy after radiotherapy, or at recurrence in patients with anaplastic glioma. Patients with recurrent glioblastoma can be treated with intravenous bevacizumab or dose-intense regimens of TMZ, but selection of optimal candidates for either therapy is unresolved. Other currently available targeted biologic agents are not part of routine management of patients with HGGs. Combination therapeutic trials of antiangiogenic and other targeted agents are ongoing in patients with HGGs. The way forward for patients with HGGs will involve treatments targeting the molecular abnormalities that are important to tumor initiation and growth. All patients with HGGs should be evaluated for clinical trial eligibility at diagnosis and upon recurrence.

Introduction

In 2004, 124,000 people in the United States were living with a malignant tumor originating in the brain or central nervous system (CNS) [1]. Each year in the US, over 14,000 persons are diagnosed with HGGs [1, 2]. HGGs account for 80% of malignant tumors of the brain and CNS [1]. HGGs are considered either grade III or IV by the World Health Organization (WHO) system. Glioblastoma (GB) is the only WHO grade IV glioma [2]. Of all HGGs, GB accounts for 53.8%; grade III tumors comprise the remainder and include anaplastic astrocytomas (AAs), anaplastic oligodendrogliomas (AOs) [1], and the less common HGGs such as anaplastic oligoastrocytomas (AOAs), anaplastic ependymomas, and anaplastic gangliogliomas.

HGGs are typically located in one of the four lobes of the brain, with the frontal lobe being the most common location and the occipital lobe, the least common [1]. Intraventricular, brainstem, cerebellar, and spinal cord localizations are rare for most HGGs except for anaplastic ependymomas. HGGs are more common in adults; the incidence increases with age up to approximately age 75 [1].

HGGs are less common than other systemic malignancies, but they cause a disproportionate amount of

morbidity and mortality. Despite currently available treatment options, the median survival ranges from 14 to 15 months for GB and from 2 to 5 years for other HGGs [3•]. The 5-year relative survival rates of HGGs in the United States (47% for AO, 27% for AA, and 4.4% for GB) highlight the need for better therapeutic strategies [1].

Standard therapy for patients with newly diagnosed HGGs includes maximal, safe surgical resection. Technological advances such as intraoperative MRI and improved surgical techniques have improved safety and the extent of surgical resection [4]. Observational studies strongly suggest that maximal surgical resection improves patient survival independent of age and Karnofsky performance score [5, Class IV]. A phase III trial using 5-aminolevulinic acid as a fluorescent label intraoperatively in patients with resectable GB resulted in a 65% rate of complete resection, compared with 35% for conventional surgical techniques [6•, Class II]. Regardless of other treatment modalities used in this trial, a gross total resection provided a survival advantage [6•, Class III].

Radiotherapy is effective for patients with HGGs. Postoperative radiotherapy improves survival in patients with GB from a range of 3–4 months to a range of 7–12 months [3•]. Fractionated external-beam radiotherapy (EBRT) is the standard of care for patients with HGGs, given as 60 Gy of partial-field EBRT delivered 5 days per week in 1.8-Gy to 2.0-Gy fractions to a 2 cm margin [4]. Intensity-modulated radiation therapy (IMRT) results in less radiation delivered to normal tissues and is likely to be comparable to EBRT, although comparative trials are lacking [7, Class IV]. Other techniques combined with conventional radiotherapy, including brachytherapy, hyperfractionation, and stereotactic radiosurgery, have not improved survival in HGG patients [3•, 4].

Even with current standard-of-care treatment including maximal surgical resection and radiotherapy with concurrent and adjuvant temozolomide (TMZ) chemotherapy, the median overall survival for GB patients is 15 months, and the median progression-free survival (PFS) is 7 months [8]. A standard of care for the other HGGs has not been firmly established. Recently reported trials using chemotherapeutic and biologic agents to treat newly diagnosed and recurrent supratentorial HGGs in adult patients are the focus of this review.

Molecular pathogenesis

Gliomagenesis is driven by dysregulated genetics and growth-factor signaling. Though morphologically indistinguishable, GBs can be separated into primary and secondary types based on their molecular profile (Fig. 1). Primary GBs occur in patients over the age of 50 years and are characterized by overexpression or mutation of the epidermal growth factor receptor (EGFR), loss of heterozygosity (LOH) on chromosome 10q, and *PTEN* mutations [2]. Secondary GBs arise from lower-grade gliomas and occur in younger patients. Secondary GBs are characterized by p53 mutations, overexpression of platelet-derived growth factor receptor (PDGFR), and abnormalities in the retinoblastoma pathway [2]. Overexpression of growth factors including EGFR and PDGFR activates the RAt Sarcoma (RAS) and phosphatidylinositol 3-kinase (PI3K)/mammalian target of rapamycin (mTOR) pathways, leading to suppression of apoptosis and increased cellular proliferation [2, 3•, 4]. Perturbations of these pathways lead to upregulation of vascular endothelial growth factor (VEGF) and angiogenesis. One mediator of glioma invasion is binding of hepatocyte growth factor/scatter factor (HGF) to the c-MET receptor. HGF also activates intracellular signaling, similar to EGFR and PDGFR [4]. Neural stem cells or progenitor cells appear to play a prominent role in tumor differentiation, proliferation, angiogenesis, and evasion of chemotherapy and targeted therapy [3•]. Developmental signaling pathways involved in neuronal and glial differentiation, including NOTCH, sonic

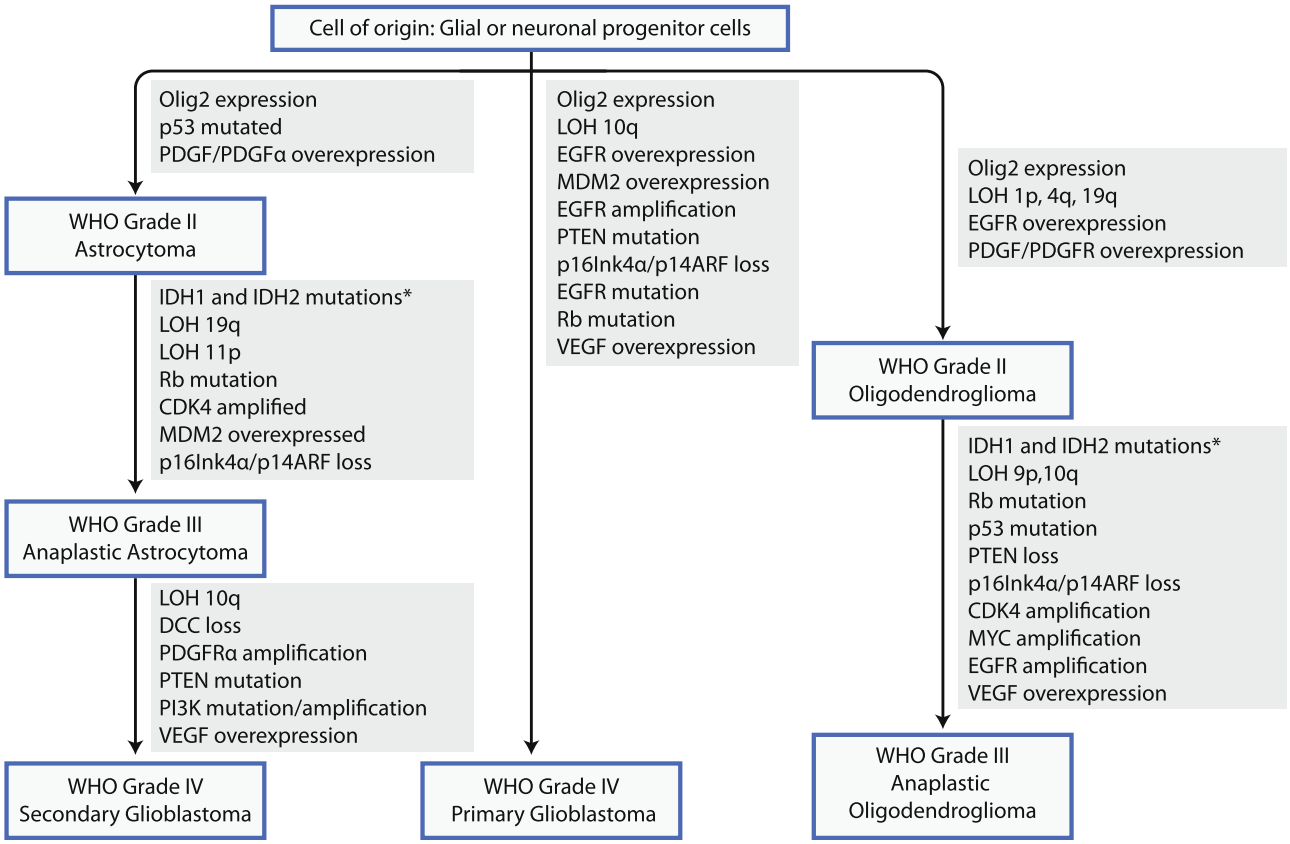

Figure 1. Genetic and chromosomal abnormalities involved in the development of high-grade gliomas. *CDK4* cyclin-dependent kinase 4, *DCC* deleted in colorectal cancer, *EGFR* epidermal growth factor receptor, *IDH1* and *IDH2* isocitrate dehydrogenase 1 and 2, *LOH* loss of heterozygosity, *MDM2* murine double minute 2, *Olig2* oligodendrocyte transcription factor 2, *PDGF* and *PDGFR* platelet derived growth factor and receptor, *PI3K* phosphatidylinositol 3-kinase, *PTEN* phosphatase and tensin homologue, *Rb* retinoblastoma gene, *VEGF* vascular endothelial growth factor, *WHO* World Health Organization. (Adapted from Wen and Kesari [3•].) *See Yan et al. [9•].

hedgehog, wingless, and the transcriptional regulator Olig 2, have also been implicated in glioma formation [3•]. Mutations in human cytosolic NADPH-dependent isocitrate dehydrogenase-1 and –2 (IDH1 and IDH2) may be an early event in glioma formation, and are found in patients with AA, AO, and secondary GB (arising from lower-grade gliomas) [9•]. Understanding the epigenetic alterations in HGGs and other regulators of gene transcription may also lead to further understanding of gliomagenesis and provide therapeutic targets [4].

Newly diagnosed glioblastoma

Chemotherapy

Before 2005, no prospective, randomized clinical trials in newly diagnosed GB had shown benefit. Meta-analyses of chemotherapy in patients with HGGs (primarily GB and AA) treated with nitrosourea-based chemother-

apeutic regimens (carmustine [BCNU] and lomustine [CCNU]) found a modest survival benefit (6%–10% at 1 year) [10]. In 2005, the European Organisation for Research and Treatment of Cancer (EORTC) and the National Cancer Institute of Canada (NCIC) Clinical Trials Group conducted a phase III trial in patients with newly diagnosed GB, comparing standard radiotherapy alone versus radiotherapy plus concurrent TMZ (75 mg per square meter of body surface area (mg/m^2) for 6 weeks during radiation therapy). Patients in the combination arm were then treated with adjuvant TMZ (150–200 mg/m^2 for 5 days of every 28 days for 6 cycles) [8]. Radiotherapy combined with TMZ was well tolerated and increased the median survival from 12.1 months to 14.6 months versus radiotherapy alone ($P<0.001$) [8, Class I]. The percentage of 2-year survivors was also increased: 26.5% in the group given radiotherapy combined with TMZ, versus 10.4% with radiotherapy alone. The 5-year analysis of the EORTC-NCIC trial reported improved survival out to 5 years for patients treated with TMZ in addition to radiotherapy [11••, Class I]. Maximal surgical resection and radiotherapy with concurrent and adjuvant TMZ is now the standard of care for patients with newly diagnosed GB.

TMZ is an alkylating chemotherapeutic agent, which adds a methyl group to the O^6, N^3, and N^7 positions of guanine on DNA [12]. Alkylation of the O^6 position of guanine results in futile cycling of the mismatch repair system in tumor cells, ultimately inducing apoptosis. Resistance to alkylating agents is mediated by the DNA repair enzyme O^6-methylguanine methyltransferase (MGMT), which repairs O^6 alkylguanine adducts [12, 13]. Hypermethylation of the promoter region of the *MGMT* gene results in loss of MGMT function. MGMT promoter methylation status is strongly associated with survival in patients with newly diagnosed GB who are treated with radiation therapy and TMZ [13]. The 2-year and 5-year survival rates for GB patients treated with TMZ in the EORTC-NCIC trial were 49% and 14% for patients with a methylated MGMT promoter, compared with 15% and 8% for patients without a methylated MGMT promoter [8, 11••]. MGMT may be a more general prognostic marker of outcomes in GBs, as patients with a methylated MGMT promoter treated only with radiation therapy without TMZ also have improved progression-free and overall survival [14]. MGMT status may have other important clinical implications. Pseudoprogression, defined as a neuroradiologic pattern suggesting progression after radiotherapy with concurrent TMZ, is seen more often in patients with a methylated MGMT promoter [15]. MGMT promoter methylation may also be associated with an increased frequency of distant tumor recurrences (defined as recurrence with no more than 20% of the enhancing tumor lying inside the 95% isodose line of the radiation field) after standard treatment with radiotherapy and TMZ [16].

Overcoming MGMT-mediated resistance to TMZ is a focus of current clinical research. As TMZ is an MGMT substrate, administering so-called dose-intense regimens using more frequent, higher, and/or more prolonged doses of TMZ could improve outcomes for GB patients. In patients whose tumors are MGMT hypermethylated, more TMZ could enhance cytotoxicity. In patients whose tumors are not hypermethylated, more TMZ could overcome drug resistance by overwhelming or depleting the MGMT [17]. Schedules of dose-dense TMZ (7 days on and 7 days off, at 150 mg/m^2 per day) and

metronomic TMZ (21 days on and 7 days off, at 100 mg/m^2 per day) are being tested in patients with newly diagnosed GB [17]. A randomized phase II trial of chemoradiotherapy with adjuvant dose-intense versus metronomic TMZ yielded promising results, with a median overall survival of 17.1 months with the dose-intense regimen and 15.1 months with metronomic TMZ [18, Class III]. A randomized phase III trial comparing metronomic TMZ versus the standard 5-day regimen has recently been completed by the Radiation Therapy Oncology Group; the results are pending. Other alkylators, such as CCNU, also deplete MGMT. In a prospective case series, CCNU was combined with TMZ after standard radiotherapy. Although hematologic toxicity was increased, the median overall survival was 23.1 months, suggesting possible synergy in MGMT depletion [19, Class IV]. Whether dose-intensification of TMZ or combination alkylator chemotherapy to overcome MGMT-mediated resistance will improve overall survival and have an acceptable toxicity profile requires further study. Determining alternative treatment approaches for patients with an unmethylated MGMT promoter is an important focus of future research.

Another mechanism of resistance to TMZ is mediated through the base excision repair (BER) system, of which poly(adenosine-diphosphate-ribose) polymerase (PARP) is a component. The BER system repairs TMZ-induced N^7 methylguanine adducts [4, 12], among other DNA adducts. PARP inhibitors, by impairing the activity of the BER system, can enhance TMZ-induced cytotoxicity [12]. PARP inhibitors are currently in early-phase clinical trials in combination with TMZ.

Another approach to delivering chemotherapy involves implanting biodegradable wafers containing BCNU (Gliadel wafers) into the tumor resection cavity. A randomized, placebo-controlled trial yielded a survival benefit of 13.9 months (Gliadel) versus 11.6 months (placebo) in patients with newly diagnosed GB; a survival advantage was still observed 2–3 years later [20, Class I]. Recent retrospective studies of patients treated with implanted BCNU wafers plus radiotherapy with concurrent and adjuvant TMZ have yielded mixed results [21, 22, Class IV]. The role of BCNU wafers in the management of glioblastoma multiforme, given the current standard of care, is unresolved.

Targeted biologic agents

Significant progress has been made in our understanding of the molecular pathogenesis and signaling pathways that drive gliomagenesis and tumor cell invasion. Dysregulation of pathways involving receptor tyrosine kinases (TKs) have been identified in GB. Whether HGGs can be inhibited with currently available agents targeting TKs and/or downstream intracellular signaling pathways is a fundamental question. Agents targeting receptor TKs such as EGFR, PDGFR, and VEGFR, and intracellular signaling pathways including mTOR, farnesyltransferase, and the RAS pathway have been tested in GB patients [3•, 4]. Targeted agents yielded disappointing results as monotherapy [3•, 4]. Poor blood–brain barrier penetration, activation of multiple TK pathways, and redundancy of intracellular signaling pathways explain some of the monotherapy failures [3•, 4]. Trials of inhibitors of protein kinase C, multiple TK receptors, and other agents that directly or indirectly

inhibit angiogenesis are ongoing in patients with newly diagnosed GB [23].

Recent phase II trials have focused on the addition of targeted agents to TMZ in patients with newly diagnosed GB. Two phase II trials evaluated the addition to TMZ of erlotinib, a specific inhibitor of the TK receptor EGFR. In these trials, erlotinib was first given during radiotherapy and was continued after radiation with adjuvant TMZ. One trial showed a relative survival advantage compared with historical controls (19.3 vs. 14.6 months), but the other trial showed no benefit of adding erlotinib to TMZ and found unacceptable treatment-related toxicity [24, Class III; 25, Class IV].

Integrins are involved with interactions between cells and their surroundings, and the α_v integrins are specifically involved in blood vessel growth in HGGs. A phase I/IIa trial combined cilengitide (which binds to integrin cell surface receptors on activated endothelial cells during angiogenesis) with TMZ. This single-arm study reported an improvement in median survival to 16.1 months without additional toxicity [26, Class IV]. The glutamate receptor system was targeted in a phase II trial using talampanel, a noncompetitive antagonist of AMPA glutamate receptors, combined with TMZ. The combination delivered a median overall survival of 18.3 months, without added toxicity [27, Class IV].

Combining outcome data across four EORTC and New Approaches to Brain Tumor Therapy (NABTT) Consortium trials suggested that adding the targeted agents talampanel, poly-ICLC, and cilengitide to standard chemoradiation resulted in improved overall survival compared with standard treatment alone (19.6 vs. 14.6 months) [28, Class IV]. Although these results are encouraging, whether the improved survival can be attributed to the targeted agents added to TMZ or to improved overall care of patients with GB requires further study. Up to this point, small-molecule, targeted agents have not yet changed day-to-day clinical practice in patients with newly diagnosed GB [23].

Combination approaches that target multiple pathways are still being developed and studied. These appear more promising than strategies targeting single molecular pathways.

Anaplastic gliomas

Anaplastic gliomas (AGs) include anaplastic astrocytoma (AA), anaplastic oligodendroglioma (AO), anaplastic oligoastrocytoma (AOA), and anaplastic ependymoma. All are classified as WHO grade III tumors [2]. These tumors, especially AA, can recur and progress to a WHO Grade IV GB within 3–5 years [2, 3•]. These tumors are often diffuse at presentation and may not be amenable to a gross total surgical resection. The inclusion of AGs in clinical trials of GB limits application of the study results to AG patients. Common clinical care of patients with AGs includes surgery followed by radiotherapy. The role of adjuvant chemotherapy in the management of AG patients is unresolved but is the focus of recent clinical trials.

Since the early 1990s, AOs and AOAs have been treated with combination chemotherapy using PCV with or without radiotherapy [29]. Chemosensitivity of oligodendroglial tumors is associated with a translocation between

the short arm of chromosome 1 and the long arm of chromosome 19 (often referred to as codeletion of 1p/19q) [29, 30••]. Codeletion of 1p/19q appears to be prognostic of tumor behavior regardless of histologic classification as AA, AO, or AOA [30••]. Patients with AGs and 1p/19q codeletion have a superior prognosis whether treated with PCV chemotherapy or radiotherapy, suggesting that 1p/19q status is prognostic rather than predictive of response [30••]. AO and AOA are similar to GB, in that MGMT promoter hypermethylation is prognostic of superior outcomes [31]. MGMT hypermethylation is also strongly associated with codeletion of 1p/19q [30••]. Two phase III trials randomizing patients to either radiotherapy alone or radiotherapy plus adjuvant or neoadjuvant PCV showed increased PFS in the groups that received chemotherapy, but no effect on overall survival [32, 33, Class II]. PCV was associated with a significant rate of hematologic toxicity (grade 3 or 4 toxicity in up to 65% of patients). Because of the uncertain benefit and the added toxicity of chemotherapy added to radiotherapy, the care of these patients varies among neuro-oncologists [34].

AAs have a shorter median survival (2 years, vs. 5 years for AOs) and are more chemoresistant than AOs [3•]. AAs are treated with maximal surgical resection followed by radiotherapy. Adjuvant chemotherapy using TMZ is often added. Whether radiotherapy with concurrent and adjuvant TMZ is effective and safe in patients with AA has not been established. Increased neurotoxicity of concurrent radiochemotherapy may be of more significance in patients with AA, given their longer survival.

A recent phase III trial, NOA-04, randomized patients with AA, AO, and AOA to radiotherapy, PCV, or TMZ at diagnosis. At relapse, patients receiving radiotherapy were treated with chemotherapy and patients treated initially with chemotherapy received radiotherapy [30••]. Regardless of the initial treatment modality, the overall survival was the same in all treatment arms [30••, Class II]. TMZ was as effective as PCV, which was associated with a higher rate of toxicity. Patients treated initially with radiotherapy had a longer PFS and better radiographic outcomes than those treated with initial chemotherapy. This study identified AAs as a distinct group based on prognosis: therapy failed in patients with AA at 32 months compared with more than 54 months for those with AO or AOA. AO and AOA had nearly identical outcomes, likely because of the restrictive central pathologic criteria and review. NOA-04 also confirmed the association of improved prognosis with codeletion of 1p/19q and hypermethylation of MGMT [30••]. This study also identified *IDH1* mutations as a marker for improved prognosis. Two current trials are evaluating radiation therapy and different schedules of concurrent and adjuvant TMZ in patients with AAs, AOs, and AOAs. One trial requires intact 1p/19q (Concomitant and Adjuvant TMZ in Nondeleted Anaplastic Astrocytoma or CATNON trial) for enrollment, and the other requires a codeletion of 1p/19q (CODEL trial).

Recurrent high-grade gliomas

Even with multi-modality treatment, most HGGs recur. Median time to progression in the EORTC-NCIC trial was 6.9 months for GB; AGs recur in 2–5 years [3•, 8]. Most patients with HGG are irradiated initially, but radiation

is an option if not used as an upfront therapy. There are no randomized trials evaluating re-irradiation in recurrent HGG. If the radiation tolerance of healthy brain tissue is exceeded, radiation necrosis may result [35]. Re-irradiation with EBRT or IMRT may be an option in selected patients. Similar to newly diagnosed patients with HGGs, brachytherapy, hyperfractionation, and stereotactic radiosurgery have not improved survival in patients with recurrent HGGs [4]. Surgery is a reasonable consideration to confirm pathology, differentiate progression from pseudoprogression, and reduce symptoms in selected patients. Surgery, radiotherapy, and the use of chemotherapeutic and biologic agents for recurrent HGGs have not demonstrated a clear survival advantage.

Although it is sometimes readily apparent by clinical worsening, recurrence can be clinically silent and may be first discovered on MRI. Recurrence must be differentiated from radiation necrosis, postsurgical effects, and effects of increasing, decreasing, or stopping steroids and antiangiogenic agents. A recent proposal outlines a definition of recurrent HGG, including updated radiographic criteria [36]. An important consideration is differentiating pseudoprogression, a neuroradiologic pattern suggesting progression after chemoradiation, from tumor progression. This pattern may be seen in over 30% of GB patients after chemoradiation [15]. No imaging technique can reliably distinguish pseudoprogression from tumor progression, although modalities such as MR perfusion, MR spectroscopy, and positron emission tomography are being investigated. Biopsy may be needed in some cases. Patients with pseudoprogression have improved survival, suggesting that the radiographic pattern may be due to improved antiglioma effects of therapy [15]. Excluding patients with pseudoprogression from clinical trials for recurrent HGGs is necessary to prevent biased trial results.

Antiangiogenic agents

HGGs are highly vascular, and extensive evidence supports angiogenesis as a key process required for tumor growth and invasion [37, 38]. Vascular endothelial growth factors (VEGFs) and their receptors are the best-characterized proangiogenic proteins in HGGs. HGGs are rapidly growing and exist in a hypoxic microenvironment, which induces secretion of VEGF [37]. Hypoxia and VEGF recruit bone marrow–derived progenitor cells necessary for tumor angiogenesis [37]. VEGF-A and its receptor VEGF receptor-2 (VEGFR-2) are the principal mediators of angiogenesis in tumor cells [37, 38]. HGGs produce a variety of other proangiogenic proteins, including basic fibroblast growth factor (bFGF), platelet derived growth factor (PDGF), and hypoxia-inducible factor 1α (HIF1α) [38]. Marked radiographic responses and improved PFS have been reported in recent trials using antiangiogenic therapies in patients with HGGs.

Bevacizumab (Avastin; Genentech, South San Francisco, CA), a humanized monoclonal antibody against VEGF, was first approved by the US Food and Drug Administration (FDA) for use in metastatic colorectal and non-small cell lung cancer and received accelerated approval for the treatment of recurrent GB in May 2009. FDA approval was based on two single-arm phase II trials combining intravenous bevacizumab and irino-

tecan in patients with recurrent HGGs [39, 40, Class IV]. The FDA's independent review of these trials determined response rates of 26% and 35%, PFS at 6 months of 29% in one trial, and a median duration of response of 3.9 months in the other [37]. These results were a significant improvement over historical rates of 6-month PFS of 9% to 15%. Steroid doses were reduced by 50% or more in over 50% of the patients enrolled in these trials. Bevacizumab was well tolerated by most patients, and adverse events were considered acceptable by the FDA. Grade 3–5 bevacizumab-related toxicities observed in these trials included systemic bleeding, CNS hemorrhage, thromboembolic complications, hypertension, proteinuria, poor wound healing, gastrointestinal perforation, and posterior reversible encephalopathy syndrome [39, 40]. The safety, tolerability and efficacy were confirmed in two subsequent phase II clinical trials with response rates of 29% and 35% and 6-month PFS rates of 43% and 50% [41•, 42•, Class IV].

There is significant interest in combination therapy including bevacizumab to improve outcomes in patients with recurrent GB. Irinotecan, a camptothecin derivative with modest efficacy as monotherapy for recurrent GB, added no significant benefit over bevacizumab alone in a randomized phase II trial of bevacizumab versus combination with irinotecan [41•, Class III]. Other agents, including oral etoposide, nitrosoureas, erlotinib, and low-dose TMZ, have been tested in phase II clinical trials in combination with bevacizumab and have not improved outcomes compared with bevacizumab monotherapy [37]. Multiple trials combining bevacizumab with targeted biologic and chemotherapeutic agents in recurrent GB are currently under way.

A variety of monofunctional and multifunctional antiangiogenic agents are being tested in newly diagnosed and recurrent GB. Cediranib, an oral pan-VEGFR receptor tyrosine-kinase inhibitor with additional activity against PDGFR β and c-Kit, recently completed phase I and II clinical trials in patients with recurrent GB. Cediranib monotherapy was associated with encouraging radiographic response rates and a steroid-sparing effect similar to bevacizumab [43]. Despite its extended spectrum of activity against VEGFR, in a single-arm phase 2 trial, cediranib did not improve the 6-month PFS (25%) or overall survival as compared with bevacizumab [43, Class IV].

Notwithstanding FDA approval and its widespread use, the optimal role of bevacizumab in recurrent GB has not been established. Bevacizumab is well tolerated and is associated with a higher response rate than other therapies for recurrent HGGs, but it appears to have no impact on overall survival, and concern has emerged that antiangiogenic therapies may alter tumor biology. Antiangiogenic agents may not treat the infiltrative component of HGGs, which may be responsible for recurrence [37]. Recent laboratory evidence suggests that VEGF inhibition may actually increase the invasive nature of tumor cells [44]. An increase in nonenhancing tumor on FLAIR MRI sequences, distant recurrence, and stable to improved enhancing disease are typical radiographic patterns observed in many patients with recurrent GB treated with bevacizumab [45, 46]. Patients who progress while being treated with bevacizumab have limited treatment options and respond poorly to salvage regimens [45, 46].

In the future, distinguishing between highly vascular tumors versus predominantly infiltrative tumors may be necessary in order to select optimal candidates for bevacizumab and other antiangiogenic therapies. Determining the optimal dose, schedule, and duration of therapy is needed. Intervals of 1, 2, 3, or even 4 weeks may be warranted, given the biologic half-life of bevacizumab. There is concern that the discontinuance of bevacizumab may be associated with a significant rebound in tumor vessel leakage or even vessel growth. Two large phase III trials evaluating bevacizumab in combination with standard treatment in patients with newly diagnosed GB are currently ongoing.

Antiangiogenic therapies also may be effective in other settings. Class I evidence supports bevacizumab as a beneficial treatment for cerebral radiation necrosis [47•, Class I].

Temozolomide

Overcoming MGMT-mediated resistance to TMZ is another strategy being tested in recurrent HGGs. The RESCUE study, a phase II trial evaluating continuous, daily TMZ (50 mg/m^2 per day) in patients with recurrent HGGs, demonstrated a median 6-month PFS of 23.9% for GBs and 35.7% for AGs [48, Class IV]. Another phase II trial evaluating continuous, daily dosing of TMZ (50 mg/m^2 per day) in recurrent GB found a median 6-month PFS of 32.5% [49, Class IV]. The preliminary results with dose-intense TMZ regimens compare favorably with pooled outcomes of other chemotherapeutic agents used in recurrent HGGs.

Another strategy to overcome MGMT-mediated resistance is direct enzymatic inhibition. O^6 benzylguanine is a pseudosubstrate of MGMT, and binding leads to proteasomal degradation of the enzyme. This strategy has been tested in a recent phase II trial in patients with recurrent, alkylator-refractory GB treated with O^6 benzylguanine and TMZ on a 1-day dosing regimen [50]. The results were disappointing, as O^6 benzylguanine did not restore TMZ sensitivity and was associated with grade IV hematologic toxicity in 48% of patients.

Recurrent anaplastic gliomas

The optimal approach for treating recurrent AGs has not been determined. A first step is to determine whether the patient's tumor has evolved into a GB. More clinical trial options are usually available for these patients. The use of standard or dose-intense TMZ or PCV if the patient has received only radiotherapy in the past is one option [30••, 48].

Bevacizumab has been shown to be well tolerated and is associated with radiographic and clinical response, with reasonable rates of PFS and time to tumor progression in patients with AGs [40, 45, Class IV]. However, AGs often do not show evidence of significant angiogenesis, explaining the frequent lack of contrast enhancement seen on MRI. They may co-opt blood vessels rather than induce vessel growth, as is seen in GB. There is concern that antiangiogenic agents may increase the invasiveness of infiltrative ana-

plastic tumor cells. This concern leaves open the optimal therapeutic role of bevacizumab in patients with recurrent AGs.

Treatment

Pharmacologic treatment

Temozolomide

Standard dosage	*Chemoradiation dosing:* 75 mg/m^2 7 days a week during radiation. *Adjuvant dosing:* 150 mg/m^2 to 200 mg/m^2 on days 1–5 of every 28-day cycle for 6–12 cycles.
Dose-intense regimens	*Dose-dense TMZ:* 150 mg/m^2 for days 1–7 and 15–21; no TMZ on days 8–14 and 22–28 of every 28-day cycle. *Metronomic TMZ:* 100 mg/m^2 for days 1–21, then 7 days off every 28-day cycle. Alternatively, 50 mg/m^2 daily on a continuous basis.
Contraindications	Hypersensitivity to TMZ or dacarbazine.
Drug interactions	Valproic acid. Other agents causing bone marrow suppression.
Main side effects	Constipation, nausea, vomiting, headache, fatigue. Thrombocytopenia and myelosuppression can occur, requiring laboratory surveillance.
Special points	Dose-intense regimens are not FDA-approved. Prophylaxis against *Pneumocystis jiroveci* is recommended during chemoradiation and should be considered in patients requiring chronic steroid administration or in patients with significant lymphopenia.

PCV (procarbazine, CCNU, vincristine)

Standard dosage	Four 6-week cycles: CCNU, 110 mg/m^2 by mouth on day 1; procarbazine, 60 mg/m^2 on days 8–21; vincristine, 1.4 mg/m^2 on days 8 and 29.
Contraindications	Hypersensitivity to any of the agents, Charcot-Marie-Tooth syndrome (vincristine), pulmonary fibrosis, preexisting myelosuppression.
Drug interactions	Procarbazine is a weak monoamine oxidase inhibitor (MAOI), and agents with MAOI activity should be avoided. CYP3A4 inducers reduce serum concentrations of vincristine, and CYP3A4 inhibitors increase serum concentrations of vincristine.
Main side effects	Cumulative myelosuppression, nausea and vomiting, hair loss, fatigue, neuropathy, CNS depression.
Special points	Toxicity often limits the duration of PCV administration. A tyramine-restricted diet is recommended, given the MAOI activity of procarbazine.

Bevacizumab

Standard dosage	10 mg/kg every 2 weeks. Decreasing dose and frequency (5 or 7.5 mg/kg every 3–4 weeks) are also possible but not approved.
Contraindications	Hypersensitivity to bevacizumab. Because of increased risk of hemorrhage, patients with thrombosis, gastrointestinal perforation, uncontrollable coagulation disorders, or serious bleeding disorders (including intracranial hemorrhage) should probably not take bevacizumab. Because of poor wound healing and wound dehiscence, bevacizumab is often held 4 weeks

	prior to and after surgical procedures. Proteinuria and hypertension can also result from bevacizumab, limiting its use in patients with uncontrolled hypertension and renal failure.
Main drug interactions	Administration with sunitinib is contraindicated owing to microangiopathic hemolytic anemia reported with this combination.
Main side effects	Hypertension, poor wound healing, proteinuria, thrombosis, gastrointestinal perforation, and hemorrhage.
Special points	Class I evidence supports the use of bevacizumab (dosed at 7.5 mg/kg every 3 weeks) in radiation necrosis of the CNS. The use of irinotecan appears to offer no benefit over bevacizumab alone, so the role of irinotecan in combination with bevacizumab is unresolved.

Disclosure

Conflicts of Interest: B. Theeler: none; M. Groves: honoraria from Genentech and Schering-Plough; payment and/or travel expenses from Genentech, Schering-Plough, and Enzon Pharmaceuticals for development of educational presentations.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

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This is an excellent review of high-grade gliomas, including molecular biology and treatment

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