Malignant gliomas account for approximately 70% of the 22,500 new cases of malignant primary brain tumors that are diagnosed in adults in the United States each year. Although relatively uncommon, malignant gliomas are associated with disproportionately high morbidity and mortality. Despite optimal treatment, the median survival is only 12 to 15 months for patients with glioblastomas and 2 to 5 years for patients with anaplastic gliomas. Recently, there have been important advances in our understanding of the molecular pathogenesis of malignant gliomas and progress in treating them. This review summarizes the diagnosis and management of these tumors in adults and highlights some areas under investigation.

**Epidemiologic Features**

The annual incidence of malignant gliomas is approximately 5 cases per 100,000 people. Each year, more than 14,000 new cases are diagnosed in the United States. Glioblastomas account for approximately 60 to 70% of malignant gliomas, anaplastic astrocytomas for 10 to 15%, and anaplastic oligodendrogliomas and anaplastic oligoastrocytomas for 10%; less common tumors such as anaplastic ependymomas and anaplastic gangliogliomas account for the rest. The incidence of these tumors has increased slightly over the past two decades, especially in the elderly, primarily as a result of improved diagnostic imaging. Malignant gliomas are 40% more common in men than in women and twice as common in whites as in blacks. The median age of patients at the time of diagnosis is 64 years in the case of glioblastomas and 45 years in the case of anaplastic gliomas.

No underlying cause has been identified for the majority of malignant gliomas. The only established risk factor is exposure to ionizing radiation. Evidence for an association with head injury, foods containing N-nitroso compounds, occupational risk factors, and exposure to electromagnetic fields is inconclusive. Although there has been some concern about an increased risk of gliomas in association with the use of cellular telephones, the largest studies have not demonstrated this. There is suggestive evidence of an association between immunologic factors and gliomas. Patients with atopy have a reduced risk of gliomas, and patients with glioblastoma who have elevated IgE levels appear to live longer than those with normal levels. The importance of these associations is unclear. Gene polymorphisms that affect detoxification, DNA repair, and cell-cycle regulation have also been implicated in the development of gliomas.

Approximately 5% of patients with malignant gliomas have a family history of gliomas. Some of these familial cases are associated with rare genetic syndromes, such as neurofibromatosis types 1 and 2, the Li–Fraumeni syndrome (germ-line p53 mutations associated with an increased risk of several cancers), and Turcot's syndrome (intestinal polyposis and brain tumors). However, most familial cases have
no identified genetic cause. Recently, an international consortium, GLIOGENE, was established to study the genetic basis of familial gliomas.

**PATHOLOGICAL FEATURES**

Malignant gliomas are histologically heterogeneous and invasive tumors that are derived from glia. The World Health Organization (WHO) classifies astrocytomas on the basis of histologic features into four prognostic grades: grade I (pilocytic astrocytoma), grade II (diffuse astrocytoma), grade III (anaplastic astrocytoma), and grade IV (glioblastoma). Grade III and IV tumors are considered malignant gliomas. Anaplastic astrocytomas are characterized by increased cellularity, nuclear atypia, and mitotic activity. Glioblastomas also contain areas of microvascular proliferation, necrosis, or both (Fig. 1 and 2). Uncommon glioblastoma variants include gliosarcomas, which contain a prominent sarcomatous element; giant-cell glioblastomas, which have multinucleated giant cells; small-cell glioblastomas, which are associated with amplification of the epidermal growth factor receptor (EGFR); and glioblastomas with oligodendrogial features, which may be associated with a better prognosis than standard glioblastomas.

Oligodendrogliomas are divided by the WHO into two grades: well-differentiated oligodendrogliomas and oligoastrocytomas (WHO grade II), and anaplastic oligodendrogliomas and anaplastic oligoastrocytomas (WHO grade III) (Fig. 1). All of these tumors may contain perinuclear halos (Fig. 2C) and a delicate network of branching blood vessels (chicken-wire pattern).

Malignant gliomas typically contain both neoplastic and stromal tissues, which contribute to their histologic heterogeneity and variable outcome. Molecular studies such as gene-expression profiling potentially allow for better classification of these tumors and separation of the tumors into different prognostic groups.

**MOLECULAR PATHOGENESIS**

Recently, there has been important progress in our understanding of the molecular pathogenesis of malignant gliomas, and especially the importance of cancer stem cells. Malignant transformation in gliomas results from the sequential accumulation of genetic aberrations and the deregulation of growth-factor signaling pathways (Fig. 1 and 3). Glioblastomas can be separated into two main subtypes on the basis of biologic and genetic differences. Primary glioblastomas typically occur in patients older than 50 years of age and are characterized by EGFR amplification and mutations, loss of heterozygosity of chromosome 10q, deletion of the phosphatase and tensin homolog on chromosome 10 (PTEN), and p16 deletion. Secondary glioblastomas are manifested in younger patients as low-grade or anaplastic astrocytomas and transform over a period of several years into glioblastomas. These tumors, which are much less common than primary glioblastomas, are characterized by mutations in the p53 tumor-suppressor gene, overexpression of the platelet-derived growth factor receptor (PDGFR), abnormalities in the p16 and retinoblastoma (Rb) pathways, and loss of heterozygosity of chromosome 10q.

Secondary glioblastomas have transcriptional patterns and aberrations in the DNA copy number that differ markedly from those of primary glioblastomas. Despite their genetic differences, primary and secondary glioblastomas are morphologically indistinguishable and respond similarly to conventional therapy, but they may respond differently to targeted molecular therapies.

High-grade oligodendrogliomas are characterized by the loss of chromosomes 1p and 19q (in 50 to 90% of patients). Progression from low-grade to anaplastic oligodendroglioma is associated with defects in PTEN, Rb, p53, and cell-cycle pathways.

**DEREGULATED GROWTH FACTOR SIGNALING**

The most common defects in growth-factor signaling involve EGFR and PDGFR (Fig. 3). Amplification of EGFR occurs almost exclusively in primary glioblastomas and is seen in approximately 40 to 50% of patients with that type of tumor. About half of the tumors with EGFR amplification express a constitutively autophosphorylated variant of EGFR, known as EGFRvIII, that lacks the extracellular ligand-binding domain (exons 2 through 7). This characteristic variant has become an important therapeutic target for kinase inhibitors, immunotoxins, and peptide vaccines. Recently, activating mutations in the extracellular domain of EGFR have been identified. PDGF signaling is a key regulator of glial development and both ligand and receptors are frequently expressed in gliomas, creating an autocrine loop that stimulates proliferation of the
Figure 1. Pathways in the Development of Malignant Gliomas.

Genetic and chromosomal alterations involved in the development of the three main types of malignant gliomas (primary and secondary glioblastomas and anaplastic oligodendroglioma) are shown. Oligodendrocyte transcription factor 2 (Olig2) (blue) and vascular endothelial growth factor (VEGF) (red) are expressed in all high-grade gliomas. Median lengths of survival (asterisks) are shown. A slash indicates one or the other or both. DCC denotes deleted in colorectal carcinoma, EGFR epidermal growth factor receptor, LOH loss of heterozygosity, MDM2 murine double minute 2, PDGF platelet-derived growth factor, PDGFR platelet-derived growth factor receptor, PI3K phosphatidylinositol 3-kinase, PTEN phoshatase and tensin homologue, and RB retinoblastoma.

ROLE OF STEM CELLS IN PATHOGENESIS AND RESISTANCE TO THERAPY

Although the genetic and signaling pathways involved in the development of malignant gliomas have important roles, the role of stem cells in glioma pathogenesis and resistance to therapy remains a topic of ongoing research.
have been relatively well characterized, the cellular origins of these tumors are unknown. The adult nervous system harbors neural stem cells that are capable of self-renewal, proliferation, and differentiation into distinctive mature cell types. There is increasing evidence that neural stem cells, or related progenitor cells, can be transformed into cancer stem cells and give rise to malignant gliomas.

Figure 2. Pathological Features of Malignant Gliomas.
Panels A and B show the histologic appearance of a glioblastoma, characterized by nuclear pleomorphism, dense cellularity, and pseudopalisading necrosis (asterisk) (Panel A, hematoxylin and eosin) as well as vascular endothelial proliferation (asterisk) and mitotic figures (arrows) (Panel B, hematoxylin and eosin). Panels C and D show the histologic features of an anaplastic oligodendroglioma, including the typical perinuclear halo (“fried egg”) appearance (Panel C, hematoxylin and eosin) and diffuse Olig2 staining (Panel D, brown color). The proliferation index can be quantified by immunohistochemical analysis with the use of Ki67 staining (Panel E, black color), and heterogeneous EGFR amplification by colorimetric in situ hybridization showing more than two signals (brown spots in nuclei) in almost all tumor cells (Panel F). (Courtesy of Ali G. Saad, M.D., Department of Pathology, Brigham and Women’s Hospital.)
by escaping the mechanisms that control proliferation and programmed differentiation (Fig. 4). These stem cells are identified by several immunocytochemical markers, such as CD133, a glycoprotein also known as prominin 1. Although stem cells account for only a minority of the cells within malignant gliomas, they appear to be critical for generating these tumors. Recent studies suggest that glioma stem cells produce VEGF and promote angiogenesis in the tumor microenvironment. In addition, tumor stem cells appear to require a vascular niche for optimal function. These observations raise the possibility that antiangiogenic therapy may inhibit the functioning of glioma stem cells.

There is growing evidence that glioma stem cells may contribute to the resistance of malignant gliomas to standard treatments (Fig. 4). Radioresistance in stem cells generally results from the preferential activation of DNA-damage response pathways, whereas chemoresistance results partly from the overexpression of O6-methylguanine–DNA methyltransferase (MGMT), the up-regulation of multidrug resistance genes, and the inhibition of apoptosis. Therapeutic strategies that effectively target stem cells and overcome their resistance to treatment will be necessary if malignant gliomas are to be completely eradicated (Fig. 4). A better understanding of the biologic differences between normal and cancer stem cells will be required to develop selective therapies that spare normal brain cells.

### DIAGNOSIS

**CLINICAL PRESENTATION**

Patients with malignant gliomas may present with a variety of symptoms, including headaches, seizures, focal neurologic deficits, confusion, memory loss, and personality changes. Although the classic headaches that are suggestive of increased intracranial pressure are most severe in the morning and may wake the patient from sleep, many patients experience headaches that are indistinguishable from tension headaches. When severe, the headaches may be associated with nausea and vomiting.

### IMAGING

The diagnosis of malignant gliomas is usually suggested by magnetic resonance imaging (MRI) or computed tomography. These imaging studies typically show a heterogeneously enhancing mass with surrounding edema. Glioblastomas frequently have central areas of necrosis and more extensive peritumoral edema than that associated with anaplastic gliomas. Functional MRJ may help define the relationship of speech and motor areas to the tumor and aid in the planning of surgery. Diffusion-weighted imaging, diffusion tensor imaging, dynamic contrast-enhanced MRI to measure vessel permeability, and perfusion imaging to measure relative cerebral blood volume are increasingly used as diagnostic aids and as a means of monitoring the response to therapy.
Proton magnetic resonance spectroscopy detects the levels of metabolites and may help differentiate a tumor from necrosis or benign lesions. In patients with malignant gliomas, this imaging technique typically shows an increase in the choline peak (reflecting increased membrane turnover) and a decrease in the N-acetyl aspartate peak (reflecting decreased neuronal cellularity), as compared with the findings in unaffected areas of the brain. Positron-emission tomography that uses...
isotopes such as $^{18}$F-fluorodeoxyglucose, $^{18}$F-fluoro-l-thymidine, $^{11}$C-methionine, and 3,4-dihydroxy-6-$^{18}$F-fluoro-l-phenylalanine is being evaluated for its usefulness in diagnosis and in monitoring the response to therapy. In up to 40% of cases, the MRI studies that are performed in the first month after radiotherapy show increased enhancement. In 50% of these cases, the increased enhancement reflects a transient increase in vessel permeability as a result of radiotherapy, a phenomenon termed “pseudoprogression,” which improves with time. Differen-

**Figure 4. Resistance Mechanisms in Glioma Cells.**

Normal neural stem cells self-renew and give rise to multipotential progenitor cells that form neurons, oligodendroglia, and astrocytes. Glioma stem cells arise from the transformation of either neural stem cells or progenitor cells (red) or, less likely, from differentiation of a oligodendrocytes or astrocytes (thin red arrows) and lead to malignant gliomas. Glioma stem cells are relatively resistant to standard treatments such as radiation and chemotherapy and lead to regrowth of the tumor after treatment. Therapies directed at stem cells can deplete these cells and potentially lead to more durable tumor regression (blue).
iating this transient effect from true progression of the cancer can be challenging initially, even with advanced imaging techniques.

### TREATMENT

#### GENERAL MEDICAL MANAGEMENT

Much of the care of patients with malignant gliomas involves general medical management. The most common problems include seizures, peritumoral edema, venous thromboembolism, fatigue, and cognitive dysfunction. Patients who present with seizures should be treated with antiepileptic drugs. Since antiepileptic drugs that induce hepatic cytochrome P-450 enzymes, such as phenytoin and carbamazepine, increase the metabolism of many chemotherapeutic agents, antiepileptic drugs that do not induce these enzymes, such as levetiracetam, are generally preferred. The use of prophylactic antiepileptic drugs in patients with malignant gliomas who have never had a seizure is controversial. The American Academy of Neurology issued a practice guideline indicating that there is no evidence that prophylactic antiepileptic drugs are beneficial and advises against their routine use in patients with brain tumors who have not had seizures.

Corticosteroids such as dexamethasone are frequently used to treat peritumoral edema. Cushing’s syndrome and corticosteroid myopathy may develop in patients who require prolonged treatment with high doses of corticosteroids. Patients with brain tumors who receive corticosteroids are at increased risk for *Pneumocystis jiroveci* pneumonitis, and prophylactic antibiotic therapy should be considered, although a recent meta-analysis did not show a benefit from this approach. As the rate of survival among patients with malignant glioma improves, long-term complications from treatment with corticosteroids, including osteoporosis and compression fractures, are becoming increasingly evident, and preventive measures, such as treatment with vitamin D, calcium supplements, and bisphosphonates, should be considered. Novel therapies such as corticotropin-releasing factor, bevacizumab (a humanized VEGF monoclonal antibody), and VEGFR inhibitors decrease peritumoral edema and may reduce the need for corticosteroids.

Patients with malignant gliomas are at increased risk for venous thromboembolism from leg and pelvic veins, with a cumulative incidence of 20 to 30%. The risk of intratumoral hemorrhage associated with anticoagulation therapy in patients with gliomas who have venous thromboembolism is low, whereas inferior vena cava filters are associated with high complication rates. Unless a patient with malignant glioma and venous thromboembolism has an intracerebral hemorrhage or other contraindications, it is generally safe to provide anticoagulation therapy for the venous thromboembolism. Low-molecular-weight heparin may be more effective and safer than warfarin.

Patients with malignant gliomas frequently experience fatigue and may benefit from treatment with modafinil or methylphenidate. Methylphenidate may also help abulia, and donepezil and memantine may reduce memory loss, although evidence supporting these approaches remains limited. Depression is underdiagnosed in patients with malignant gliomas, and antidepressants and psychiatric support are often invaluable.

#### SPECIFIC THERAPY FOR NEWLY DIAGNOSED MALIGNANT GLIOMAS

The standard therapy for newly diagnosed malignant gliomas involves surgical resection when feasible, radiotherapy, and chemotherapy (Table 1). Malignant gliomas cannot be completely eliminated surgically because of their infiltrative nature, but patients should undergo maximal surgical resection whenever possible. Surgical debulking reduces the symptoms from mass effect and provides tissue for histologic diagnosis and molecular studies. Advances such as MRI-guided neuro-navigation, intraoperative MRI, functional MRI, intraoperative mapping, and fluorescence-guided surgery have improved the safety of surgery and increased the extent of resection that can be achieved. The value of surgery in prolonging survival is controversial, but patients who undergo extensive resection probably have a modest survival advantage. Stereotactic biopsies should be performed only in patients who have inoperable tumors that are located in critical areas.

Radiotherapy is the mainstay of treatment for malignant gliomas. The addition of radiotherapy to surgery increases survival among patients with glioblastomas from a range of 3 to 4 months to a range of 7 to 12 months. Conventional radiotherapy consists of 60 Gy of partial-field external-beam irradiation delivered 5 days per week in fractions of 1.8 to 2.0 Gy. After standard radio-
therapy, 90% of the tumors recur at the original site.\textsuperscript{65} Strategies to increase the radiation dose to the tumor with the use of brachytherapy\textsuperscript{66} and stereotactic radiosurgery\textsuperscript{67,68} have failed to improve survival. Newer chemotherapeutic agents,\textsuperscript{69} targeted molecular agents,\textsuperscript{20} and antiangiogenic agents\textsuperscript{70} may enhance the effectiveness of radiotherapy.

Patients who are older than 70 years of age have a worse prognosis than younger patients and represent a particular challenge. Among these patients, radiotherapy produces a modest benefit in median survival (29.1 weeks) as compared with supportive care (16.9 weeks).\textsuperscript{71} Since older patients often tolerate radiotherapy less well than younger patients, an abbreviated course of radiotherapy (40 Gy in 15 fractions over a period of 3 weeks)\textsuperscript{72} or chemotherapy with temozolomide (an oral alkylating agent with good penetration of the blood–brain barrier) alone\textsuperscript{73} may be considered, since the outcomes with these approaches are similar to the outcomes with conventional radiotherapy regimens.

Chemotherapy is assuming an increasingly important role in the treatment of malignant gliomas. Although early studies of adjuvant chemotherapy for malignant gliomas with the use of nitrosoureas failed to show a benefit,\textsuperscript{63,74} two meta-analyses have suggested that adjuvant chemotherapy results in a modest increase in survival (a 6 to 10% increase in the 1-year survival rate).\textsuperscript{75,76}

The European Organisation for Research and Treatment of Cancer (EORTC) and the National Cancer Institute of Canada (NCIC) conducted a phase III trial comparing radiotherapy alone (60 Gy over a period of 6 weeks) with radiotherapy and concomitant treatment with temozolomide (75 mg per square meter of body-surface area per day for 6 weeks), followed by adjuvant temozolomide therapy (150 to 200 mg per square meter per day for 5 days every 28 days for 6 cycles), in patients with newly diagnosed glioblastomas.\textsuperscript{64} As reported by Stupp et al., the combination of radiotherapy and temozolomide had an acceptable side-effect profile and, as compared with radiotherapy alone, increased the median survival (14.6 months vs. 12.1 months, P<0.001).\textsuperscript{64} In addition, the survival rate at 2 years among the patients who received radiotherapy and temozolomide was significantly greater than the rate among the patients who received radiotherapy alone (26.5% vs. 10.4%).\textsuperscript{64} Establishing radiotherapy with concomitant and adjuvant temozolomide as a useful combination for newly diagnosed glioblastomas.

MGMT is an important repair enzyme that contributes to resistance to temozolomide. In a companion study to the EORTC–NCIC study reported by Stupp et al., tumor specimens from the pa-

### Table 1. Summary of Current Treatments for Malignant Gliomas.\textsuperscript{6}

<table>
<thead>
<tr>
<th>Type of Tumor</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newly diagnosed tumors</td>
<td>Maximal surgical resection, plus radiotherapy, plus concomitant and adjuvant TMZ or carmustine wafers (Gliadel)†</td>
</tr>
<tr>
<td>Glioblastomas (WHO grade IV)</td>
<td>Maximal surgical resection, with the following options after surgery (no accepted standard treatment): radiotherapy, plus concomitant and adjuvant TMZ or adjuvant TMZ alone‡</td>
</tr>
<tr>
<td>Anaplastic astrocytomas (WHO grade III)</td>
<td>Maximal surgical resection, with the following options after surgery (no accepted standard treatment): radiotherapy alone, TMZ or PCV with or without radiotherapy afterward, radiotherapy plus concomitant and adjuvant TMZ, or radiotherapy plus adjuvant TMZ‡‡</td>
</tr>
<tr>
<td>Anaplastic oligodendrogliomas and anaplastic oligoastrocytomas (WHO grade III)</td>
<td>Maximal surgical resection, with the following options after surgery (no accepted standard treatment): radiotherapy alone, TMZ or PCV with or without radiotherapy afterward, radiotherapy plus concomitant and adjuvant TMZ, or radiotherapy plus adjuvant TMZ‡‡</td>
</tr>
<tr>
<td>Recurrent tumors</td>
<td>Reoperation in selected patients, carmustine wafers (Gliadel), conventional chemotherapy (e.g., lomustine, carmustine, PCV, carboplatin, irinotecan, etoposide), bevacizumab plus irinotecan, experimental therapies‡‡</td>
</tr>
</tbody>
</table>

\* Data are from Sathornsumetee et al., Furnari et al.,\textsuperscript{63} Chi and Wen,\textsuperscript{20} and Sathornsumetee et al.\textsuperscript{21} PCV denotes procarbazine, lomustine (CCNU), and vincristine, and TMZ temozolomide.

† Radiotherapy is administered at a dose of 60 Gy given in 30 fractions over a period of 6 weeks. Concomitant TMZ is administered at a dose of 75 mg per square meter of body-surface area per day for 42 days with radiotherapy. Beginning 4 weeks after radiotherapy, adjuvant TMZ is administered at a dose of 150 mg per square meter per day on days 1 to 5 of the first 28-day cycle, followed by 200 mg per square meter per day on days 1 to 5 of each subsequent 28-day cycle, if the first cycle was well tolerated.

‡ PCV therapy consists of lomustine (CCNU), 110 mg per square meter, on day 1; procarbazine, 60 mg per square meter, on days 8 to 21; and vincristine, 1.5 mg per square meter (maximum dose, 2 mg), on days 8 and 29.

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patients were examined for epigenetic silencing of the MGMT gene.\textsuperscript{15} MGMT promoter methylation silences the gene, thus decreasing DNA repair activity and increasing the susceptibility of the tumor cells to temozolomide. Patients with glioblastoma and MGMT promoter methylation (45% of the total) who were treated with temozolomide had a median survival of 21.7 months and a 2-year survival rate of 46%. In contrast, patients without MGMT promoter methylation who were treated with temozolomide had a significantly shorter median survival of only 12.7 months and a 2-year survival rate of 13.8%.\textsuperscript{15} Currently, temozolomide is used in the treatment of glioblastomas regardless of MGMT promoter methylation status. However, if the importance of MGMT promoter methylation is confirmed by the results of an ongoing study by the Radiation Therapy Oncology Group (RTOG 0525), patients with unfavorable methylation status may be selected for other treatments in future investigations. Studies of methylation status may be selected for other (RTOG 0525), patients with unfavorable

Therapy for Anaplastic Gliomas

Anaplastic astrocytomas are treated with radiotherapy and either concurrent and adjuvant temozolomide (as for glioblastomas) or adjuvant temozolomide alone. Currently, there are no findings from controlled trials that support the use of concurrent temozolomide in patients with anaplastic astrocytomas.

Anaplastic oligodendrogliomas and anaplastic oligoastrocytomas are an important subgroup of malignant gliomas that are generally more responsive to therapy than are pure astrocytic tumors.\textsuperscript{79} A codeletion of chromosomes 1p and 19q,\textsuperscript{79} mediated by an unbalanced translocation of 19p to 1q,\textsuperscript{80} occurs in 61 to 89% of patients with anaplastic oligodendrogliomas and 14 to 20% of patients with anaplastic oligoastrocytomas. Tumors in patients with the 1p and 19q codeletion are particularly sensitive to chemotherapy with PCV — procarbazine, lomustine (CCNU), and vincristine — with response rates of up to 100%, as compared with response rates of 23 to 31% among patients without the deletion of chromosomes 1p and 19q.\textsuperscript{81,82} The reason for the increased chemosensitivity of tumors in patients with the 1p and 19q codeletion is unclear. One study suggested that 1p loss is associated with decreased levels of stathmin and an increased sensitivity to nitrosoureas.\textsuperscript{83} The status of chromosomes 1p and 19q, rather than standard histologic assessment, is now used as an eligibility criterion in studies involving patients with anaplastic oligodendrogliomas and anaplastic oligoastrocytomas, reflecting a paradigm shift in the design of clinical trials for patients with these tumors.

Two large phase III studies of PCV chemotherapy with radiotherapy, as compared with radiotherapy alone, in patients with newly diagnosed anaplastic oligodendrogliomas or anaplastic oligoastrocytomas, have been reported.\textsuperscript{84,85} In both studies, the addition of chemotherapy to radiotherapy increased the time to tumor progression by 10 to 12 months but did not improve overall survival (median, 3.4 and 4.9 years).\textsuperscript{84,85} The failure of chemotherapy to increase survival may be partly explained by the fact that patients who initially received radiotherapy alone subsequently received chemotherapy when they had a relapse, so that most patients in both groups eventually received chemotherapy. In both studies, patients with the codeletion of 1p and 19q had improved survival as compared with those without the codeletion of 1p and 19q. Although most studies involving patients with anaplastic oligodendrogliomas or anaplastic oligoastrocytomas were conducted with PCV chemotherapy, temozolomide is likely to have similar activity and less toxicity\textsuperscript{79}; however, studies directly comparing the two regimens have not been performed.

Therapy for Recurrent Malignant Gliomas

Despite optimal treatment, nearly all malignant gliomas eventually recur. For glioblastomas, the median time to progression after treatment with radiotherapy and temozolomide is 6.9 months.\textsuperscript{84} If the tumor is symptomatic from mass effect, re-
operation may be indicated (Table 1). However, surgery performed in selected patients results in only limited prolongation of survival.86

The usefulness of radiotherapy for recurrent malignant gliomas is controversial.87 Although some reports have suggested that fractionated stereotactic reirradiation88 and stereotactic radiosurgery68 may be beneficial, selection bias may have influenced these results.

The value of conventional chemotherapy for recurrent malignant gliomas is modest. In general, chemotherapy is more effective for anaplastic gliomas than for glioblastomas.79,87 Temozolomide was evaluated in a phase II study involving patients with recurrent anaplastic gliomas who had previously been treated with nitrosoureas; the study showed a 35% response rate. The 6-month rate of progression-free survival was 46%,89 comparing favorably with the 31% rate of progression-free survival at 6 months for therapies that were reported to be ineffective.90 In contrast, temozolomide has only limited activity in patients with recurrent glioblastomas (response rate, 5.4%; 6-month rate of progression-free survival, 21%).91 Other chemotherapeutic agents that are used for recurrent gliomas include nitrosoureas, carboplatin, procarbazine, irinotecan, and etoposide. Carmustine wafers have modest activity, increasing the median survival by approximately 8 weeks in patients with recurrent glioblastomas.92

**INVESTIGATIONAL THERAPIES**

**TARGETED MOLECULAR THERAPIES**

The improved understanding of the molecular pathogenesis of malignant gliomas has allowed a more rational use of targeted molecular therapies (Fig. 3).18,20,21 Particular interest has focused on inhibitors that target receptor tyrosine kinases such as EGFR,93 PDGFR,94 and VEGFR,52 as well as on signal-transduction inhibitors targeting mTOR,95,96 farnesyltransferase,97 and PI3K (Table 2). Single agents have only modest activity, with response rates of 0 to 15% and no prolongation of 6-month progression-free survival.3,20,21 These disappointing results are due to several factors. Most malignant gliomas have coactivation of multiple tyrosine kinases,98 as well as redundant signaling pathways, thus limiting the activity of single agents. In addition, many of these agents have poor penetration across the blood–tumor barrier. There has been considerable interest in identifying molecular features of the tumor that predict a response, so that patients who are most likely to benefit can be selected for a particular treatment. EGFR inhibitors appear to be more effective in patients who have tumors with EGFRvIII mutations and intact PTEN than in patients who do not have these molecular changes99; patients who have tumors with increased activity of the PI3K–Akt pathway, as indicated by an increase in phosphorylated Akt, generally do not have a response.100 Current experimental strategies to increase the effectiveness of targeted molecular therapies include the use of a single agent targeted against several kinases, combinations of agents that inhibit complementary targets such as EGFR and mTOR (Table 2 and Fig. 5A through 5D), and targeted agents combined with radiotherapy and chemotherapy.3,18,20,21

**ANTIANGIOGENIC AGENTS**

Malignant gliomas are among the most vascular of human tumors,18 making them especially attractive targets for angiogenesis inhibitors.29 Although older antiangiogenic agents such as thalidomide had only modest activity,101 newer and more potent angiogenesis inhibitors show promising activity. In preliminary studies, treatment with the combination of bevacizumab and irinotecan was associated with a low incidence of hemorrhage and response rates of 57 to 63% among patients with malignant gliomas (Fig. 5E through 5H).102,103 Some of the improvement that is seen on radiographic images may be artifactual, caused by reduced vascular permeability and decreased contrast enhancement as a result of the inhibition of VEGF. However, this regimen also has antitumor activity, as evidenced by the fact that it increased the 6-month rate of progression-free survival to 46% among patients with recurrent glioblastomas,102,103 as compared with a 6-month rate of progression-free survival of 21% for patients who were receiving treatment with temozolomide.91 Recently, a large, randomized phase II trial of bevacizumab alone and bevacizumab with irinotecan was completed. Preliminary results confirmed the safety of bevacizumab and showed an increase in the 6-month rate of progression-free survival to 35.1% for patients receiving bevacizu-
Table 2. Selected Investigational Treatments for Malignant Gliomas.*

<table>
<thead>
<tr>
<th>Type of Treatment</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Convection-enhanced surgical delivery of pharmacologic agent</td>
<td>Cintredekin besudotox</td>
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<tr>
<td>Drugs to overcome resistance to TMZ</td>
<td></td>
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<tr>
<td>Dose-dense TMZ</td>
<td></td>
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<tr>
<td>MGMT inhibitors</td>
<td>O6-benzylguanine</td>
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<tr>
<td>PARP inhibitors</td>
<td>BSI-201, ABT-888</td>
</tr>
<tr>
<td>New chemotherapies</td>
<td>RTA744, ANG1005</td>
</tr>
<tr>
<td>Antiangiogenic therapies</td>
<td></td>
</tr>
<tr>
<td>Anti-αvβ5 integrins</td>
<td>Cilengitide</td>
</tr>
<tr>
<td>Anti-hepatocyte growth factor</td>
<td>AMG-102</td>
</tr>
<tr>
<td>Anti-VEGF</td>
<td>Bevacizumab, aflibercept (VEGF-Trap)</td>
</tr>
<tr>
<td>Anti-VEGFR</td>
<td>Cediranib, pazopanib, sorafenib, sunitinib, vandetinib, vatalanib, XL184, CT-322</td>
</tr>
<tr>
<td>Other agents</td>
<td>Thalidomide</td>
</tr>
<tr>
<td>Targeted molecular therapies</td>
<td></td>
</tr>
<tr>
<td>Akt</td>
<td>Perifosine</td>
</tr>
<tr>
<td>EGFR inhibitors</td>
<td>Erlotinib, gefitinib, lapatinib, BIBW2992, nimotuzumab, cetuximab</td>
</tr>
<tr>
<td>FTI inhibitors</td>
<td>Tipifarnib, lonafarnib</td>
</tr>
<tr>
<td>HDAC inhibitors</td>
<td>Vorinostat, depsipeptide, LBH589</td>
</tr>
<tr>
<td>HSP90 inhibitors</td>
<td>AT13387</td>
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<tr>
<td>Met</td>
<td>XL184</td>
</tr>
<tr>
<td>mTOR inhibitors</td>
<td>Everolimus, sirolimus, temsirolimus, deforolimus</td>
</tr>
<tr>
<td>PI3K inhibitors</td>
<td>BEZ235, XL765</td>
</tr>
<tr>
<td>PKCβ</td>
<td>Enzastaurin</td>
</tr>
<tr>
<td>PDGFR inhibitors</td>
<td>Dasatinib, imatinib, tandutinib</td>
</tr>
<tr>
<td>Proteasome</td>
<td>Bortezomib</td>
</tr>
<tr>
<td>Raf</td>
<td>Sorafenib</td>
</tr>
<tr>
<td>Src</td>
<td>Dasatinib</td>
</tr>
<tr>
<td>TGF-β</td>
<td>AP12009</td>
</tr>
<tr>
<td>Combination therapies</td>
<td>Erlotinib plus temsirolimus, gefitinib plus everolimus, gefitinib plus sorafenib plus temsirolimus, erlotinib, or tipifarnib, pazopanib plus lapatinib</td>
</tr>
<tr>
<td>Immunotherapies</td>
<td></td>
</tr>
<tr>
<td>Dendritic cell and EGFRvIII peptide vaccines</td>
<td>DCVax, CDX-110</td>
</tr>
<tr>
<td>Monoclonal antibodies</td>
<td>131I-anti-tenascin antibody</td>
</tr>
<tr>
<td>Gene therapy</td>
<td></td>
</tr>
<tr>
<td>Other therapies</td>
<td>131I-TM-601</td>
</tr>
</tbody>
</table>

* Data are from Sathornsumetee et al.,7 Furnari et al.,8 Chi and Wen,9 and Sathornsumetee et al.10 EGFR denotes epidermal growth factor receptor, FTI farnesyltransferase, HDAC histone deacetylase, HSP90 heat-shock protein 90, MGMT O6-methylguanine−DNA methyltransferase, mTOR mammalian target of rapamycin, PARP poly (ADP-ribose) polymerase, PDGFR platelet-derived growth factor receptor, PI3K phosphatidylinositol 3-kinase, PKCβ protein kinase C β, TGF transforming growth factor, TMZ temozolomide, and VEGFR vascular endothelial growth factor receptor.
mab alone and 50.2% for patients receiving the combination of bevacizumab and irinotecan. A phase II trial of the pan-VEGFR inhibitor cediranib in patients with recurrent glioblastomas showed response rates in excess of 50% and prolongation of the 6-month rate of progression-free survival to approximately 26%. These agents also decrease peritumoral edema, potentially allowing for a reduction in corticosteroid requirements. Since antiangiogenic agents may have synergistic activity with radiotherapy, there is increasing interest in combining them with radiotherapy and temozolomide in patients with newly diagnosed glioblastomas. As noted previously, glioma stem cells produce VEGF and require a vascular niche for optimal function. Antiangiogenic agents may therefore also target glioma stem cells.

**OTHER THERAPIES**

Other investigational therapies for malignant gliomas include chemotherapeutic agents that cross the blood–tumor barrier more effectively, gene therapy, peptide and dendritic-cell vaccines, radiolabeled monoclonal antibodies against the extracellular matrix protein tenascin, synthetic chlorotoxins (131I-TM-601), and infusion of radiolabeled drugs and targeted toxins into the tumor and surrounding brain by means of convection-enhanced delivery (Table 2).

**PROGNOSTIC FACTORS**

The most important adverse prognostic factors in patients with malignant gliomas are advanced age, histologic features of glioblastoma, poor Karnofsky performance status, and unresectable tumor. There are ongoing efforts to identify biologic and genetic alterations in the tumors that may provide additional prognostic information, as well as guidance in making decisions about optimal therapy.
Recently, there has been important progress in the treatment of malignant gliomas and in our understanding of the molecular pathogenesis of these tumors and the critical role that stem cells play in their development and resistance to treatment. As our understanding of the molecular correlates of response improves, it may be possible to select the most appropriate therapies on the basis of the patient’s tumor genotype. These advances provide real opportunities for the development of effective therapies for malignant gliomas.

SUMMARY

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This article is dedicated to the memories of Elizabeth Atkins, Will Kraft, and John Kenney.

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