Therapy for recurrent malignant glioma in adults

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Malignant gliomas are the most common form of primary brain tumors in adults. Although the prognosis remains poor, there has been recent progress in the treatment of these tumors. Standard therapy for patients with this disease will be reviewed, together with more novel approaches such as targeted molecular therapies, angiogenesis inhibitors, immunotherapies, gene therapies and intratumoral therapies.


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Malignant gliomas are the most common type of primary brain tumor, with an annual incidence of approximately 5 in 100,000 people per year [1,2]. Over 12,000 new cases are diagnosed in the USA each year [1,2]. Although they are relatively uncommon, malignant gliomas account for a disproportionate amount of cancer-related morbidity and mortality. Glioblastoma multiforme (GBM) account for approximately 60–70% of malignant gliomas, anaplastic astrocytomas (AA) 10–15%, anaplastic oligodendrogliomas (AO), and anaplastic oligoastrocytomas (AOA) 10%, while less commonly occurring tumors such as anaplastic ependymomas and anaplastic gangliogliomas account for the remaining [1,2]. Although the treatment options for patients with recurrent malignant glioma remain limited, there have been important advances in recent years. This review summarizes the current status of therapy for these tumors in adults and highlights some of the areas under active investigation.

Therapy for newly diagnosed malignant glioma

Standard therapy for newly diagnosed malignant glioma involves surgical resection, when feasible, external-beam radiation therapy (RT) (approximately 60 Gy in 30 fractions) and chemotherapy [3–7]. Early clinical trials of adjuvant chemotherapy were limited by small sample size and other methodologic issues. However, two meta-analyses found adjuvant chemotherapy to be beneficial [8,9]. Fine and coworkers found that adjuvant chemotherapy produced an absolute increase in survival of 10.1% at 1 year and 8.6% in 2 years [8]. Patients with AA benefited more than GBM patients. In a second, more recent meta-analysis of 12 clinical trials, Stewart and coworkers also found significant prolongation of survival with adjuvant chemotherapy [9]. At 1 year, patients receiving chemotherapy had a 15% decrease in relative risk of death, 6% absolute increase in survival (from 40 to 46%) and a 2-month increase in median survival time.

Temozolomide (TMZ) is an alkylating agent with activity against malignant glioma. Based on preclinical evidence that TMZ has additive activity when combined with RT [10], Stupp and coworkers conducted a Phase II study in which 64 patients with newly diagnosed GBM were treated with TMZ 75 mg/m²/day for 6 weeks with concomitant fractionated RT (60 Gy; 2 Gy for 5 days per week for 6 weeks) followed by TMZ adjuvant therapy (200 mg/m²/day for 5 days every 28 days for six cycles) [5]. This regimen was well tolerated and the median survival of 16 months was significantly better than the historic median survival for GBM of 9–12 months. Based on these promising results, the European Organization for Research and Treatment of Cancer (EORTC) and the National Cancer Institute of Canada (NCIC) conducted a randomized Phase III trial (EORTC Study 26981) of 573 patients, comparing this regimen of concomitant and adjuvant TMZ and RT with RT alone in patients with newly diagnosed GBM.
This study showed that the combination of TMZ with RT was well tolerated and resulted in a survival benefit. The median survival of patients treated with TMZ plus RT was increased compared with RT alone (14.6 vs. 12.1 months; $p < 0.0001$). In addition, patients receiving TMZ with RT had a significantly higher percentage of patients surviving at 2 years (26%) than patients receiving RT alone (10%). Although 68% of RT patients received chemotherapy at recurrence (56% received TMZ), their outcome was inferior to those patients who received concomitant and adjuvant TMZ. This landmark study conclusively demonstrated for the first time that adjuvant chemotherapy is of benefit in patients with GBM.

Recently, Westphal and coworkers completed a large Phase III, multicenter placebo-controlled trial that demonstrated that biodegradable wafers containing 3.85% carmustine (Gliadel® wafers) improved survival in patients with newly diagnosed GBM [11]. Intention-to-treat median survival was 13.9 months for the carmustine wafer-treated group compared with 11.6 months for the placebo-treated group ($p = 0.03$). Adverse events were comparable for the two groups, except for an increased incidence of cerebrospinal fluid leak and intracranial hypertension in the carmustine wafer-treated group. Based on these results, Gliadel® wafers were approved in 2003 by the US Food and Drug Administration (FDA) for use in patients with newly diagnosed GBM.

Despite these treatments, patients with GBM have a median survival of approximately 9–14 months, while those with AA have a median survival of 24 to 36 months [12]. For patients with malignant gliomas whose tumors recur, the median time to tumor progression (MTP) is only 9 weeks with current therapy [3,12].

**Therapy for recurrent malignant glioma**

The treatment of recurrent malignant glioma has been discussed in several recent reviews [6,7,13–16]. As standard therapy for newly diagnosed malignant glioma evolves, therapy for recurrent malignant glioma is also changing (TABLE 1).

**Surgery**

For patients with symptomatic recurrent malignant glioma in noneloquent areas and good performance status, surgical resection may improve the patient's well-being and allow time for additional therapy [15]. The benefit of surgery in prolonging survival is more controversial since there is inevitable selection bias [14]. In one study, the median high-quality survival period (Karnofsky performance status [KPS] ≥ 70) after reoperation in patients with GBM was 18 weeks [17]. Surgical debulking may also potentially improve response to chemotherapy. Keles and coworkers found that patients with recurrent GBM, in whom the volume of residual disease (VRD) after surgery was less than 10 cm$^3$ at the start of chemotherapy, had a 6-month progression-free survival (PFS) rate of 32%, compared with 3% for patients with a VRD larger than 15 cm$^3$ [18]. Patients in whom the VRD was smaller than 10 cm$^3$ also had an improved 1-year survival rate of 37%, compared with 18% for patients with a VRD larger than 15 cm$^3$.

**Radiation therapy**

Patients with malignant glioma who received external-beam RT at the time of diagnosis usually recur within 2 cm of the original tumor site [19]. Reirradiation with standard external-beam RT may benefit selected patients [20–22], but only occasionally leads to increased survival [14]. The role of RT in patients with recurrent malignant glioma is usually limited to brachytherapy, stereotactic radiosurgery (SRS) or stereotactic radiotherapy (SRT) [15–23], techniques that attempt to deliver a high dose of radiation to the tumor volume, while limiting the radiation dose to the surrounding normal brain.

**Brachytherapy**

Brachytherapy involves either the placement of low-activity radioactive seeds in the wall of the cavity at the time of surgery, or the use of stereotactic techniques to place catheters containing radioactive isotopes (e.g., $^{125}$I) within brain tumors, enabling tumoricidal doses of radiation to be delivered to defined volumes, while reducing the risk of radiation injury to surrounding normal tissues [24]. Stereotactic brachytherapy is usually limited to unifocal, well-defined, supratentorial tumors less than 4 cm in diameter that do not involve corpus callosum, brain stem, or ependymal surfaces. Due to these restrictions, only 20–30% of patients with malignant glioma are suitable candidates. A number of Phase II studies suggested that stereotactic brachytherapy may prolong survival in patients with recurrent malignant glioma, with median survivals from recurrence of approximately 1 year [24,25]. However, it is likely that much of the observed benefit may be related to selection bias since only patients with small, circumscribed tumors were eligible for the technique [26]. A prospective randomized trial of this technique in patients with newly diagnosed GBM failed to demonstrate any benefit [27].

Some reports suggest that placement of permanent $^{125}$I seeds into the wall of the surgical cavity produces similar results to stereotactic brachytherapy [28,29]. In one recent study involving 38 patients, the MTP was 16 weeks and median survival 52 weeks [29]. However, the same issues of selection bias arise in these studies and both forms of brachytherapy have been largely replaced by SRS and SRT, which have the advantage of being noninvasive.

A newer form of brachytherapy currently undergoing evaluation is GliaSite® (Proxima Therapeutics). This is an inflatable balloon catheter that is placed in the resection cavity at the time of tumor debulking. Low-dose-rate radiation is delivered with an aqueous solution of organically bound $^{125}$I (lornax [sodium3-($^{125}$I)-iodo-4-hydroxybenzenesulfonate]), which is temporarily introduced into the balloon portion of the device via a subcutaneous port [30]. At least 40–60 Gy is delivered to the tumor bed. Although a preliminary report suggested a promising median survival of 12.7 months in previously treated patients who underwent GliaSite therapy [30], a more recent study showed a median time to radiographic failure and median survival of only 3.3 and 7.5 months, respectively. These modest results were similar those obtained with SRS [31].
Stereotactic radiosurgery & radiotherapy

SRS is a technique used to treat small (usually <4 cm) radio-
graphically well-defined tumors with a large single fraction of
ionizing radiation using stereotactically directed narrow beams.
Similar to brachytherapy, it significantly increases the radiation
dose delivered to the tumor bed while sparing normal brain.
Radiosurgery can be performed with high-energy x-rays pro-
duced by linear accelerators, with $\gamma$-rays from the gamma knife
and with charged particles, such as protons, produced by cyclo-
trons. SRT involves the precise delivery of fractionated radiation
to the tumor volume [32]. It combines the accuracy of SRS
with the reduced toxicity of fractionated irradiation and is more
suitable for larger tumors and tumors involving eloquent areas
of the brain [33]. Several uncontrolled studies suggested that
SRS increased median survival in patients with recurrent malig-
ant glioma to 8–11 months [25,33,34]. These results were simi-
lar to those obtained with stereotactic brachytherapy [25]. There
is interest in enhancing the therapeutic effect of SRS with

table 1. Summary of therapies for recurrent malignant glioma.

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Subtypes</th>
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<tbody>
<tr>
<td>Radiation therapy</td>
<td>Brachytherapy, Gliosite, stereotactic radiosurgery, stereotactic radiotherapy</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>Temozolomide, carmustine, lomustine, irinotecan, carboplatin, etoposide. Combinations: procarbazine + lomustine + vincristine; temozolomide + irinotecan; temozolomide + cisplatin; carboplatin + etoposide</td>
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<tr>
<td>Targeted molecular therapy</td>
<td>EGFR inhibitors:</td>
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<tr>
<td></td>
<td>- Gefitinib, erlotinib, lapatinib (dual EGFR and ErbB-2 inhibitor), AEE788 (EGFR + VEGFR inhibitor)</td>
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<td>PDGF inhibitors:</td>
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<td>- Imatinib mesylate</td>
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<td>mTOR inhibitors:</td>
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<td>- Temsirolimus, everolimus, rapamycin, AP23573</td>
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<td>Farnesytransferase inhibitors:</td>
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<td>- Tipifarnib, lonafarnib</td>
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<td>VEGFR inhibitors:</td>
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<td>- PTK 787, sorafenib, AEE788</td>
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<td></td>
<td>Raf kinase inhibitor:</td>
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<td>- Sorafenib</td>
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<td></td>
<td>Histone deacetylase inhibitors:</td>
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<td></td>
<td>- Deacipressidine, suberyoanilide hydroxamic acid</td>
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<tr>
<td>Intratumoral therapy</td>
<td>Gliadel wafers, intratumoral chemotherapy, PE3800Q, IL-4 and Pseudomonos exotoxin (NBI-3001), PE-38 Pseudomonos exotoxin (directed against EGFR), $^{131}$I-TM-601 (directed against chloride channels)</td>
</tr>
<tr>
<td>Antiangiogenic therapy</td>
<td>Thalidomide, interferon-$\alpha$, cyclooxygenase-2 inhibitors, Revlimid (CC-5013), endostatin, carboxamidotriazole, VEGFR inhibitors, LY317615 (PKC-$\beta$ inhibitor), celengitide ($\alpha$V$\beta$3 and $\alpha$V$\beta$5 inhibitor), antiangiogenic (metronomic) chemotherapy</td>
</tr>
<tr>
<td>Gene therapy</td>
<td>Chemosensitization genes, immunostimulatory genes, tumor suppressor genes, oncolytic viruses</td>
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<tr>
<td>Immunotherapy</td>
<td>Monoclonal antibodies, cytokines, adoptive immunotherapy, vaccines (dendritic cell and peptide)</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>Tamoxifen, cis-retinoic acid</td>
</tr>
</tbody>
</table>

Investigational therapies. EGFR: Epidermal growth factor receptor; IL: Interleukin; mTOR: Mammalian target of rapamycin; PDGF: Platelet-derived growth factor receptor; VEGFR: Vascular endothelial growth factor receptor.

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lar to those obtained with stereotactic brachytherapy [25]. There
is interest in enhancing the therapeutic effect of SRS with

chemotherapy, radiation enhancers and biologic agents such as
marimistat, a matrix metalloprotease inhibitor that may pre-
vent invasion [14,32,35]. As with brachytherapy, it is likely that
selection bias may account for much of the perceived benefit
[32]. The preliminary results of the Radiation Therapy Oncology
Group (RTOG) 93–05 trial, which suggest that the addi-
tion of SRS to newly diagnosed GBM does not improve sur-
vival, are also consistent with the limited benefit of SRS in
patients with malignant glioma [32]. These results are perhaps
not surprising given the inability of focal irradiation to treat
infiltrating tumor cells distant from the main tumor mass.

Novel radiation therapies

A variety of novel RT strategies are being explored, including
boron neutron capture therapy (BNCT) and targeted radio-
therapy. In boron neutron capture therapy, $^{10}$B carriers such as
L-p-boronophenylalanine-fructose are administered to patients and
taken up by the tumor. These patients then receive irradiation
with neutrons of the appropriate energy. A nuclear reaction occurs producing high-energy α-particles and recoiling 7Li nuclei, killing tumor cells [36,37]. Although this is a promising therapy, much work remains before its potential is realized. Another area of interest is the use of targeted radiotherapy in which radionuclides, such as 131I-labeled monoclonal antibodies (mAbs) [38,39] or other compounds that target brain tumors, are administered into the postoperative surgical cavity. These agents will be discussed later in this review.

**Chemotherapy for anaplastic astrocytoma & glioblastoma**

Chemotherapy for recurrent malignant glioma is discussed in several recent reviews [6,7,13–16,40]. Prior to the introduction of TMZ, nitrosoureas such as carmustine and the combination of procarbazine, lomustine and vincristine (PCV; 6-week cycles of lomustine 110 mg/m² orally day 1, procarbazine 60 mg/m² orally days 8–21, and vincristine 1.4 mg/m² intravenously days 8 and 29; maximum 2 mg) were the standard chemotherapeutic regimens for recurrent glioma [6,7,13–15]. Overall response rates for these agents ranged from 10 to 30%, but in general the durations of response were brief [6,13,14,41]. Many of the studies were performed before the widespread availability of magnetic resonance imaging (MRI), and frequently patients were not stratified according to histology, often making interpretation of the data difficult. In one relatively recent study of PCV in patients with recurrent GBM, there were 3% complete responses (CR), 8% partial responses (PR) and 25% stable disease (SD) [42]. MTP and survival were 13 and 33 weeks, respectively [42]. Procarbazine alone also has modest activity. In one Phase II study of procarbazine (150 mg/m²/day for 28 days every 8 weeks) of 35 patients, two patients had CR, seven PR and 11 SD [43]. Platinum compounds, alone or in combination with other agents such as etoposide (e.g., carboplatin 300 mg/m² days 1 and 3 and etoposide 100 mg/m² days 1–5 every 4 weeks), also have modest activity with PR rates ranging from 11 to 21% [13,44]. Other agents with modest activity include cyclophosphamide [45] and etoposide [46].

Attempts to improve the activity of these agents with intraarterial delivery [47], dose escalation with autologous bone marrow transplantation [48,49] and myeloprotectants such as thymidine [50], blood–brain barrier disruption with agents such as the bradykinin analog RMP-7 [51], combination with agents to increase tumor oxygenation [52], and with cytokines such as interferon (IFN)-α, have been largely unsuccessful [53].

**Temozolomide**

Temozolomide is an orally administered alkylating agent with activity against malignant glioma. It is a prodrug that spontaneously converts to the active alkylating agent 5-(3-methyltriazen-1-yl) imidazole-4-carboximide (MTIC) under physiologic conditions. The cytotoxicity of TMZ is principally mediated through methylation of DNA at the O⁶ position of guanine [54–57]. In clinical studies, TMZ has 100% oral bioavailability and readily penetrates the blood–brain barrier. Based on the encouraging results of Phase I and II studies [54], a randomized trial was conducted to compare the efficacy of TMZ with procarbazine in patients with GBM at first relapse [57]. Patients were randomized to TMZ administered orally once daily for 5 days at a starting dose of either 200 mg/m²/day (no prior chemotherapy) or 150 mg/m²/day (prior chemotherapy) every 28 days, or procarbazine 150 mg/m²/day for 28 days every 56 days. TMZ performed better than procarbazine in terms of PFS, overall survival and objective response to treatment, although the differences were modest. The 6-month PFS was 21% in the TMZ group compared with 8% in the procarbazine group (p = 0.008). In comparison, the 6-month PFS for GBM patients in eight negative Phase II trials from MD Anderson Cancer Center was only 15% [58]. Median PFS was 2.89 months with TMZ compared with 1.97 months with procarbazine. The median overall survival for the intent-to-treat population of TMZ recipients with GBM (7.34 months) was longer than for procarbazine recipients (5.82 months). A total of 5.4% of TMZ patients and 5.3% of procarbazine patients had a PR, while 40.2% of TMZ patients and 27.4% of procarbazine patients had SD. The overall response rate (PR + SD) was 45.6% in the TMZ group and 32.7% in the procarbazine group [57]. The most common grade 3 or 4 toxicities in the TMZ group were headache (10%), thrombocytopenia (7%), neutropenia (4%), fatigue (3%), vomiting (4%) and nausea (4%). Quality of life was significantly better in the TMZ group.

In another trial, the efficacy of TMZ for AA at first relapse was evaluated in a Phase II study consisting of 162 patients [56]. TMZ was administered once daily for 5 days every 28 days at a starting dose of either 200 mg/m²/day in patients who had received no prior chemotherapy or 150 mg/m²/day in patients who had received prior chemotherapy. Of the patients, 8% experienced a CR, 27% had a PR and 26% had SD, producing an overall response rate of 61%. The 6-month PFS was 46% compared with 31% from the MD Anderson database of eight negative Phase II trials for recurrent AA [58]. The MTP was 5.4 months and the median survival 14.6 months. Both overall response and maintenance of progression-free status was associated with health-related quality of life benefits, independent of steroid use [59]. Based on these results, TMZ was approved by the FDA for the treatment of recurrent AA in 1999.

Over the past several years, TMZ has become the treatment of choice for patients with recurrent malignant glioma. However, the responses tend to be modest and short lived. Several different schedules have been evaluated but none have been clearly superior to the standard regimen [60]. With the increasing use of concomitant and adjuvant TMZ with RT in newly diagnosed malignant glioma [4,5], it is likely that TMZ will have a smaller role in the future in the treatment of these tumors at recurrence.

TMZ has also been evaluated in combination with a number of other chemotherapeutic and biologic agents to improve the therapeutic benefit [16,40]. Phase I studies of the drug in combination with procarbazine [61], etoposide [62], and irinotecan [63,64] have been completed and Phase II studies are in progress.
or undergoing final analysis. A Phase II study of carmustine (150 mg/m²) and TMZ (550 mg/m³) every 6 weeks in patients with recurrent glioma showed only modest activity and significant toxicity [65]. Two studies combining TMZ with biologic agents have shown modest benefit. The North American Brain Tumor Consortium (NABTC) conducted a Phase II study of TMZ 150 or 200 mg/m²/day, days 1–5, and cis-retinoic acid (CRA) 100 mg/m²/day, days 1–21, every 28 days [66]. Retinoids such as CRA produce apoptosis, differentiation and inhibition of proliferation of glioma cells [66]. Of the 88 eligible patients (40 GBM and 44 anaplastic glioma [AG]), there were two CRs (3%) and eight PRs (12%). The 6-month PFS was increased for both GBM (30%) and AG (50%) compared with 15% for GBM and 31% for AG from the MD Anderson Cancer Center [58]. In a second study, Groves and coworkers conducted a Phase II trial of TMZ with the matrix metalloproteinase inhibitor marimastat, which potentially inhibits glioma invasion. A total of 44 patients with recurrent GBM were treated with TMZ 150–200 mg/m² days 1–5, and marimastat 50 mg days 8–28 was administered at 28-day intervals [67]. The 6-month PFS was increased at 39%. However, there was moderate toxicity with almost half the patients experiencing troublesome joint and tendon pain. A recent Phase II study of cisplatin (40 mg/m² days 1 and 2) and TMZ (200 mg/m² days 2–6 every 4 weeks) suggested that this regimen may be more active than TMZ alone. The 6-month PFS was 35% for GBM and 69% for AA [68]. Brandes and coworkers examined another schedule of cisplatin and TMZ in chemotherapy-naïve recurrent GBM patients (cisplatin 75 mg/m² on day 1, TMZ 130 mg/m² bolus followed by nine doses of 70 mg/m² every 12 h from day 2; total of 5 days) every 4 weeks. They found a similar 6-month PFS of 34% [69]. A recent small Phase II study of TMZ with liposomal doxorubicin in patients with recurrent GBM also showed modest activity with a 6-month PFS of 32% [70].

Irinotecan
Irinotecan is a camptothecin derivative which acts as a prodrug that undergoes enzymatic hydrolysis to 7-ethyl-10-hydroxy camptothecin (SN-38), a potent topoisomerase I inhibitor [16,71]. In preclinical studies, irinotecan demonstrated significant antitumor activity against human glioma cell lines and xenografts [71–73], and showed promising antitumor activity in an early study in patients with recurrent malignant glioma [74]. In this study, 60 patients received 125 mg/m² of irinotecan weekly for 4 weeks followed by a 2-week rest. Of the patients, 15% achieved a PR and 55% had SD. The toxicities observed were less than expected and the area under the plasma concentration time curve (AUC) for irinotecan and SN-38 were much lower than for systemic tumors. Irinotecan is metabolized by cytochrome P450 3A4 (CYP3A4) to an inactive metabolite 7-ethyl-10-[4-N-95-aminopectaneicid]-1-piperidino[carboxyloxy]camptothecin, while SN-38 is deactivated by glucuronidation by the uridine diphosphate glucuronosyltransferase isoenzyme UGT1A1 [73]. Both of these inactivating enzymes are induced by antiepileptic drugs such as phenytoin and carbamazepine. This induction may have accounted for the lack of toxicity and the low AUC reported in the initial study [74]. Recently, two Phase I studies of irinotecan in malignant glioma patients receiving enzyme-inducing antiepileptic drugs (EIAEDs) were completed. The NABTC examined a once-ever-3-weeks schedule and found the maximum tolerated dose (MTD) for irinotecan to be 750 mg/m² for patients on EIAEDs compared with 350 mg/m² for patients not on EIAEDs [75]. The New Approaches to Brain Tumor Therapy (NABTT) consortium evaluated a schedule in which patients were treated for 4 consecutive weeks followed by a 2-week break. For patients receiving EIAEDs, the MTD was 411 mg/m² compared with 117 mg/m² for patients not on EIAEDs [76]. These results are consistent with prior experience with chemotherapeutic agents such as paclitaxel (Taxol®, Bristol–Myers Squibb), in which patients taking EIAEDs required much higher doses of the chemotherapeutic agents to achieve therapeutic levels compared with those not taking EIAEDs [73].

Several Phase II studies evaluating the efficacy of irinotecan in patients with recurrent malignant glioma using doses appropriate for the concomitant AED have been published, suggesting that this drug has only modest activity [16]. The NABTT consortium conducted a Phase II trial of irinotecan using the weekly schedule in 18 patients with a variety of malignant gliomas [71]. There was one CR (6%), no PRs and five SDs (28%). The regimen was not well tolerated and a third of patients had to be removed due to toxicity. The North Central Cancer Treatment Group (NCCTG) conducted a Phase II study involving 64 malignant glioma patients. A total of 32 were treated using the weekly dosing schedule (Trial A) and 32 using the 3-weekly schedule (Trial B). Two of 30 evaluable patients (7%) from Trial A and four patients (13%) in Trial B experienced a response [73]. Raymond and coworkers conducted a Phase II trial of irinotecan in chemotherapy-naïve patients with GBM using 350 mg/m² every 3 weeks. A total of 25 patients received irinotecan before RT and 27 received the drug at first relapse [77]. Valproic acid (a non-EIAED) was used for seizure prophylaxis. Overall, there was only one PR (2.2%). Surprisingly, although valproic acid inhibits the glucuronidation of SN-38 in Wistar rats, there was no increase in toxicity or irinotecan or SN-38 levels in this study, raising the possibility of a species difference in valproic acid’s ability to inhibit glucuronidation of SN-38. Cloughesy and coworkers treated 35 patients with an intrapatient dose-escalation design in which patients with recurrent malignant glioma initially received 300–400 mg/m² of irinotecan every 3 weeks [78]. The dose was then escalated by steps of 100 mg/m² in subsequent courses depending on the patients’ tolerance. Only three patients (8%) had a PR and 12 patients (35%) had SD [78]. Interestingly, patients whose tumors showed extreme drug resistance to SN38 in an in vitro assay had a much worse outcome than patients with more chemosensitive tumors, suggesting that this form of testing may have some utility [79]. Chamberlain treated 40 malignant glioma patients with the 3-weekly regimen beginning at 400 mg/m² and increasing to 500 mg/m² after one cycle. There
was no attempt to stratify patients according to the type of AED. No responses were observed [80]. The NABTC recently completed accrual to a Phase II trial of irinotecan using the 3-week schedule. The final results are pending.

In summary, these studies suggest that single-agent irinotecan has only modest activity in malignant glioma, with response rates ranging from 0 to 13%, and no significant prolongation of 6-month PFS [16]. However, irinotecan may still have a potential role when used in combination with RT and other chemotherapeutic agents. Irinotecan has also been evaluated in combination with a number of other agents such as carmustine, TMZ and thalidomide. Recently, a Phase II study of carmustine and irinotecan in malignant glioma was completed [81]. Carmustine (100 mg/m^2) was administered on day 1 of each 6-week cycle and irinotecan was administered on days 1, 8, 15 and 22 at 225 mg/m^2 for patients receiving EIAEDs and at 125 mg/m^2 for those not on these medications. Of 39 recurrent malignant glioma patients, there was one CR, four PRs and 40% SD. The results were felt to be comparable with those of irinotecan alone, but with greater toxicity [81]. The preliminary results of the NABTC Phase I/II study of TMZ and irinotecan for recurrent malignant glioma appear promising [63]. Patients

![Figure 1. Axial T1-weighted contrast-enhanced magnetic resonance images of a 35-year-old woman with recurrent glioblastoma. The patient achieved a partial response. (A) and (B) were taken before therapy with temozolomide and irinotecan; (C) and (D) were obtained after 4 months of treatment and show a partial response.](image-url)
received 150 mg/m²/day for 5 days every 28 days of TMZ, together with either 200 mg/m² of irinotecan every 2 weeks if they were not receiving EIAEDs and 500 mg/m² of irinotecan every 2 weeks if they were receiving EIAEDs. The regimen was fairly well tolerated and of the 20 non-EIAED GBM patients evaluable for response, 25% achieved PR and 50% had SD (FIGURE 1). The 6-month PFS for the GBM patients was 38% (95% confidence interval [CI]: 22, 66%). In a second study evaluating the combination of TMZ and irinotecan, 83% of GBM patients and 100% of AA patients were reported to have either SD or a response [64]. However, the interpretation of this study is limited by the fact that only patients who received two cycles of therapy were considered evaluable.

Other chemotherapeutic agents

In addition to irinotecan, there is significant interest in other camptothecin derivatives for malignant glioma. Clinical trials are currently in progress for gimetecan, edotecarin and kariotecin. A large number of other chemotherapeutic agents are currently undergoing evaluation including oxaliplatin, pyrazoloacridine, SarCNU (a nitrosourea with potentially less likelihood to produce pulmonary toxicity than carmustine) and epothilones such as BMS-247550 [7,8,2,3]. Recently, Weller and coworkers reported activity with the combinations of nimustine (90 mg/m² intravenously on day 1) and tenoposide (60 mg/m² intravenously on days 1–3) and nimustine with cytarabine (120 mg/m² intravenously on days 1–3) [84]. Pegylated liposomal doxorubicin has also been reported to have some activity, although the 6-month PFS from a recent Phase II trial was only 15% [85].

Chemotherapy for anaplastic oligodendroglioma & anaplastic oligoastrocytoma

AO and AOA account for over 10% of malignant gliomas [1,2]. In 1988, Caincross and Macdonald reported that eight consecutive patients with AO responded to the combination of PCV [86], suggesting that these were chemosensitive tumors. Subsequent studies have confirmed that both AO and AOA are chemosensitive tumors, responding to the combinations of PCV or intensive PCV (6-week cycles of lomustine 130 mg/m² orally day 1, procarbazine 75 mg/m²/day orally days 8–21, and vincristine 1.4 mg/m² intravenously on days 8 and 29 with no maximum dose) [87–90]. In a Phase II study of intensive PCV for patients with new or recurrent AO, there was a 75% overall response rate, with 38% CR. The time to tumor progression for complete responders was greater than 25.2 and 14.2 months for partial responders [87]. Intensive PCV results in greater toxicity than standard PCV and is now less commonly used. Oligodendrogliomas also respond to other alkylators such as carmustine, lomustine, thiopeta, melphalan, dacarbazine, cisplatin and carboplatin [88,91].

In an attempt to improve disease control and postpone RT in patients with newly diagnosed AO, Abrey and coworkers evaluated the therapeutic efficacy of high-dose chemotherapy with stem cell rescue [49]. Patients were treated with three to four cycles of intensive PCV followed by high-dose thiotepa with stem cell rescue. The transplant was generally well tolerated and median PFS was 69 months. However, nearly half the patients did not proceed to the high-dose chemotherapy due to an inadequate response to induction chemotherapy and early relapse. Further studies using this approach, incorporating molecular analysis to select patients with chemosensitive tumors, appear warranted.

Temozolomide

Although PCV is generally considered to be the standard therapy for patients with AO and AOA, it is associated with cumulative myelosuppression, nausea, fatigue and weight loss. TMZ is better tolerated by patients than PCV. However, to date, PCV has not been directly compared with TMZ in these tumors. Recently, several studies have suggested that TMZ has activity in AO [92–95]. Chinot and coworkers treated 47 patients with recurrent AO and AOA who had previously received PCV with standard-dose TMZ. Of the patients, 14.9% had a CR, 25.9% PR and 42.5% SD [93]. The 6-month PFS was 53% and median PFS 7.5 months. This study suggests that TMZ has activity in patients with recurrent AO and AOA previously treated with PCV, and that this activity is superior to other standard chemotherapeutic agents. In a similar study, the EORTC (Study 26972) treated 32 patients with recurrent oligodendroglioma who had received PCV with TMZ [94]. Of the patients, 25% had an objective response and the median PFS was 8 months [94]. More recently, the EORTC conducted a Phase II trial of TMZ as first-line chemotherapy in recurrent oligodendroglial tumors (EORTC Study 26971) [95]. A total of 38 patients received TMZ for 12 months. There were ten CRs (26.3%), ten PRs (26.3%) and nine SDs (31%). The MTP for all patients was 10.4 months, with 40% of patients free from progression at 1 year. The treatment was well tolerated and the response rates suggest that TMZ can be considered as an alternative to PCV for patients with AO and AOA. The EORTC is planning to conduct a randomized Phase III study comparing PCV with TMZ, which will determine whether the two treatments are truly equivalent.

Molecular characterization of oligodendrogliomas

The reason for the sensitivity of oligodendrogliomas to chemotherapy is an area of active investigation. Caincross and coworkers observed that approximately two-thirds of AO had deletion of chromosomes 1p and 19q, and that these tumors were sensitive to PCV chemotherapy, with a 100% response rate and a median survival of greater than 10 years [92,96,97]. Patients with deletion of 1p only were also chemosensitive, but survival was less than for tumors with deletion of both 1p and 19q. In contrast, tumors with intact 1p had a response rate to chemotherapy of only 18–33%, and those with intact 1p and no p53 mutations had a particularly poor prognosis [97]. Other studies have shown that loss of 1p and 19q may also predict the sensitivity of AO to RT, as well as the sensitivity of low-grade oligodendrogliomas to chemotherapy [92]. This ability to molecularly characterize AO into chemosensitive tumors with good
prognosis (tumors with loss of 1p and 19q) and chemoresistant tumors with poor prognosis (intact 1p and no p53 mutations) represents a major advance in the classification of brain tumors. It potentially allows a patient’s therapy to be tailored based on the genetic findings and has led to the search for similar molecular markers in other brain tumors [90,92].

**O6-alkylguanine-DNA alkyltransferase inhibition**

The killing of glioma cells by alkylating agents such as carmustine and TMZ is prevented in part by the DNA repair enzyme O6-alkylguanine-DNA alkyltransferase (AGT). Pre-exposure to other alkylating agents may potentially increase the therapeutic index of nitrosoureas or TMZ by saturating all the copies of AGT present in the tumor cells [98]. In one study, patients with GBM were treated with 100 mg/m2 of procarbazone on days 1–5, 80 mg/m2 of carmustine on days 3–5, and 1.4 mg/m2 of vincristine on day 3, every 8 weeks. The overall response rate of 58.6% (10.3 CR, 19 PR and 29.3% SD) and 6-month PFS of 42.3% were relatively high, but at the cost of significant toxicity [98].

O6-benzylguanine (O6-BG) is an inhibitor of AGT and potentially increases the antitumor activity of chemotherapeutic agents. Quinn and coworkers conducted a Phase II trial of O6-BG at an intravenous dose of 120 mg/m2 followed 1 h later by 40 mg/m2 of carmustine, with cycles repeated at 6-week intervals [99]. Of the 18 patients who were treated, none had a PR and only four had SD of greater than 8 weeks. Moreover, there was significant hematologic toxicity. The combination of O6-BG with carmustine therefore appears ineffective, at least at the dose schedule examined. Currently, combinations of O6-BG with TMZ and O6-BG with carmustine wafers are being evaluated in clinical trials [100].

**Intratumoral therapy**

The toxicities and poor CNS penetration associated with systemic chemotherapy have led to a number of different approaches aimed at delivering therapeutic agents directly into the tumor bed, potentially increasing the exposure of tumor cells to the drug and reducing the likelihood of systemic complications. These include chemotherapeutic agents, immunotoxins and radionuclides [101,102].

**Gliadel® wafers**

The most widely studied intratumoral therapy involves biodegradable carmustine wafers (Gliadel® wafers) implanted into the surgical bed of patients with malignant gliomas. In a prospective placebo-controlled trial of 222 patients with recurrent GBM requiring reoperation, patients were randomized to receive surgically implanted biodegradable polymer discs with or without 3.85% carmustine [103]. Median survival for the group who received carmustine wafers was 31 weeks, compared with 23 weeks for the group that received placebo polymers (hazard ratio: 0.67; p = 0.006). The 6-month survival was greater in patients who received the carmustine polymer (mortality 44 vs. 64% for control patients; p = 0.02). Infections were more common in the carmustine polymer group, but the difference did not reach statistical significance [103]. This trial lead to approval of carmustine wafers by the FDA for the treatment of recurrent malignant glioma. These carmustine wafers are fairly well tolerated, although the survival benefit they offer is modest and their use precludes patients from enrolling into most clinical trials. To improve on the effectiveness of these wafers, the NABTT consortium conducted a dose-escalation study and found the MTD to be 20% of carmustine by weight [104]. Additional studies are needed to establish the efficacy of high-dose carmustine polymers. The combination of carmustine polymers with TMZ and O6-BG are also undergoing investigation.

**Other intratumoral therapies**

There is also interest in the intratumoral administration of other chemotherapeutic agents. Intratumoral injection of DTI-015 (carmustine in 100% ethanol to facilitate a rapid and thorough saturation of the tumor with the drug) appeared to be safe and resulted in SD in 72% of evaluable patients, although the median duration was only 10.5 weeks [105]. Intratumoral convection-enhanced delivery of paclitaxel has also been evaluated. In a small study, this treatment produced high response rates (five CRs and six PRs in 15 patients), but was associated with a significant incidence of complications [106]. Stereotactic intratumoral implantation of 5-fluorouracil-releasing microspheres appears to be safe and is undergoing evaluation both as a single agent and in combination with RT [107].

In addition to chemotherapeutic agents, there is also interest in intratumoral administration of other therapies [16]. Malignant glioma cells overexpress interleukin (IL)-13 [108]. Several Phase I/II studies of a recombinant fusion protein of IL-13 with a mutated form of Pseudomonas exotoxin (IL-13 PE38QQR) administered by convection therapy following resection of the tumor are nearing completion [109,110]. Convection therapy involves the slow infusion over a period of several days of the agent through catheters placed stereotaxically into the brain parenchyma surrounding the surgical cavity. This increases drug diffusion through the brain, allowing it to reach infiltrating tumor cells. This therapy appears reasonably safe and responses have been observed in Phase I studies. Based on these promising results, a randomized Phase III study comparing this approach with carmustine wafers for GBM patients at first relapse is currently in progress (PRECISE Trial). Glioma cells also express high levels of IL-4 and Phase I/II trials of a chimeric recombinant fusion protein of IL-4 and Pseudomonas exotoxin (NBI-3001) are in progress [111–113]. Preliminary results suggest that it is moderately well tolerated. Other intratumoral agents being evaluated include chimeric proteins of transforming growth factor (TGF)-α and a mutated Pseudomonas exotoxin PE-38 (TP-38) directed against the epidermal growth factor receptor (EGFR) [114], and an 131I-radiolabeled peptide derived from scorpion venom that binds to chloride channels in gliomas (131I-TM-601) [115].
Targeted molecular therapy

There has recently been increasing understanding of the molecular changes occurring in malignant gliomas [2,16,116–118]. Molecular analyses of gliomas show a stepwise progression of genetic changes involving overexpression of proto-oncogenes and loss of tumor suppressor genes. Low-grade astrocytomas (World Health Organization [WHO] grade 2) tend to have inactivating mutations of p53 and overexpression of platelet-derived growth factor (PDGF) and its receptor (PDGFR). Progression to AA (WHO grade 3) is associated with inactivation of the p16-cdk4-Rb pathway and allelic loss of 19q, while progression further to a secondary glioblastoma (WHO grade 4) is associated with loss of chromosome 10 and other changes. Primary glioblastomas, which arise de novo, often have loss of PTEN, together with amplification, mutation or overexpression of the EGFR. There is increasing work on molecular profiling of malignant gliomas using a variety of different techniques. These approaches are beginning to enable genes important in tumor progression to be identified [119]. In addition, morphologically indistinguishable malignant gliomas can be differentiated into molecular subtypes that may eventually be used for identifying potential targets for treatment [120,121], patient stratification in clinical studies [122], and for determining prognosis [123].

Recently, tyrosine kinase inhibitors have shown promising therapeutic potential in several systemic cancers [124]. The prototypic targeted molecular agent is imatinib mesylate (STI-571; Gleevec®, Novartis), a small molecule inhibitor of the Abl, c-kit and PDGFR tyrosine kinases. It has demonstrated significant antitumor activity in chronic myelogenous leukemia (CML) by inhibiting the Abl tyrosine kinase and in gastrointestinal stromal tumors (GIST) by inhibiting c-kit [124]. The success of imatinib in these tumors demonstrates the potential of these agents in tumors with well-defined molecular targets. Although the complexity of the molecular abnormalities in malignant glioma and the redundancy of the signaling pathways make it unlikely that single agents will achieve the same success as imatinib in CML, there has been significant interest in this approach [125–131]. Recently, several of the first-generation trials evaluating targeted molecular agents in malignant glioma have reached maturity, and it is possible to draw some preliminary conclusions (FIGURE 2). In general, these agents have been well tolerated, but unfortunately only a small minority of patients have benefited.

EGFR inhibitors

The EGFR is an attractive therapeutic target in glioblastomas [116,126,129,132]. The EGFR gene is amplified in 30–40% of primary GBM, resulting in overexpression of EGFR [2]. Some of

![Figure 2. Main signaling pathways in malignant glioma and the site of action of targeted molecular agents. X indicates site of inhibition. FTIs: Tipifarnib, lonafarnib; Raf inhibitors: Sorafenib; TKIs: EGFR – gefitinib, erlotinib, lapatinib, AEE788; PDGFR – imatinib; VEGFR – PTK787, AEE788, sorafenib; mTOR inhibitors: Temsirolimus, everolimus, sirolimus, AP23573. EGFR: Epidermal growth factor (receptor); Erk: Extracellular signal-regulated kinase; FTI: Farnesyltransferase inhibitor; IGF: Insulin-like growth factor; MEK: Mitogen-activated protein kinase; PDGF: Platelet-derived growth factor (receptor); PI3K: Phosphoinositol-3-kinase; PTEN: Phosphatase and tensin homolog; TKI: Tyrosine kinase inhibitor; VEGF: Vascular endothelial growth factor (receptor).](attachment:image.png)
the tumors with EGFR amplification also have gene rearrangements resulting in a constitutively active mutant (EGFR vIII). Overactivity of the EGFR pathway results in cell proliferation, increase in tumor invasiveness, motility and angiogenesis, and inhibition of apoptosis, and may be associated with a worst prognosis [133]. Several small-molecule tyrosine kinase inhibitors of the EGFR are being evaluated in malignant glioma (FIGURE 2).

The NABTC conducted a Phase I/II study of gefitinib (ZD1839; Iressa®, AstraZeneca) in patients with recurrent malignant glioma [134]. As expected, the MTD in patients taking EIAEDs was significantly increased (1500 mg/day) compared with patients not on EIAEDs (500 mg/day) since the drug is metabolized by CYP3A4. A total of 55 patients in the Phase II study were treated at the MTD appropriate for the AED they were taking. There were seven PRs, although the 6-month PFS was not increased (13% for GBM and 33% for AG) (FIGURE 3). In a second Phase II study, 53 patients with recurrent GBM were treated with 500 mg/day of gefitinib initially [132]. The dose was then escalated in each patient until a maximum dose of 1000 mg/day was reached. There were no objective tumor responses, although only 21% of patients had measurable disease. The 6-month PFS was 13%. As in other cancers, there did not appear to be a correlation between EGFR expression and response. In both studies, the drug was well tolerated, with rash and diarrhea being the most common toxicities. Uhmm and coworkers conducted a Phase II trial of gefitinib in patients with newly diagnosed GBM [135]. Although overall there was no improvement in survival compared with historic controls, patients who experienced diarrhea and rash survived longer than those patients without these complications. This suggests that patients with a higher drug exposure may benefit from this therapy, and highlights the importance of adequate dosing. Recently, responses to gefitinib in patients with non-small cell lung cancer were correlated with the presence of activating mutations in the ATP pocket of the tumor cells [136]. The prevalence of these mutations in malignant glioma is unclear, but preliminary studies have failed to demonstrate the presence of these mutations in glioma cell lines to date [136].

Several studies are currently underway evaluating the related EGFR inhibitor erlotinib (OSI-774; Tarceva®, Genentech). The NABTC conducted a Phase II study in 45 patients with recurrent malignant gliomas not on EIAEDs. There were two PRs and two SDs, and there was no prolongation of 6-month PFS [137]. In contrast to this largely negative study, Prados and coworkers reported that in a Phase I study of erlotinib with or without TMZ, there were six PRs, two minor responses (MRs) and two SDs in 25 evaluable patients [138]. Similar results have been observed by Vogelbaum and coworkers [139]. Studies with other EGFR inhibitors, including lapatinib (GW-572016, a dual EGFR and ErbB-2 inhibitor) and AEE788 (EGFR and vascular endothelial growth factor [VEGF] inhibitor) are being planned.

In general, the studies with EGFR inhibitors show that these agents are well tolerated. However, the responses tend to be limited and short lived. As with other targeted agents, it is likely that EGFR inhibitors may be more effective when combined with other therapies such as RT, chemotherapy, or other targeted molecular agents [16,126,129,140].

**PDGFR inhibitors**

There is increasing evidence that overexpression and activation of PDGFRs may be an important factor contributing to the transformed phenotype of malignant gliomas [116,141,142]. The PDGFA and -B ligands are expressed in most glioma cell lines and fresh surgical isolates of malignant gliomas. The PDGF-α receptor subunit is overexpressed in virtually all glioma cell lines and primary cultures of malignant gliomas, while the PDGF-β receptor subunit is frequently expressed within glioma tumor cells and endothelial cells [141,142]. Kilic and coworkers demonstrated that imatinib, a potent inhibitor of PDGFR-α and -β, significantly inhibited the growth of U343 and U87 GBM cell lines, *in vitro* and *in vivo* in heterotopic glioma models [142]. These data suggest that inhibition of PDGF autocrine loop with imatinib may be of therapeutic value in patients with malignant glioma. The NABTC conducted a Phase I study of imatinib in patients with recurrent malignant glioma and meningioma (NABTC 99–08) [143]. Since imatinib is metabolized by CYP3A4, patients were stratified into EIAED and non-EIAED groups. The MTD for patients not taking EIAEDs was 1200 mg/day of imatinib without developing dose-limiting toxicity (DLT). The AUC0–24 and plasma half-lives of imatinib in patients taking EIAEDs were significantly less than 50% of
that in patients not taking EIAEDs. Phase II studies of imatinib in recurrent glioma are currently being conducted by the NABTC, EORTC and NCCTG. Preliminary results of the EORTC study showed three PRs and six SDs over 6 months in 51 patients, suggesting that the drug has modest activity [144]. The poor ability of imatinib to cross the blood–brain barrier may potentially limit its effectiveness [145]. Dreseman combined imatinib 400 mg/day with hydroxyurea (1000 mg/day) in the hope that hydroxyurea would improve CNS penetration of imatinib [146]. Preliminary results appear promising, with four PRs and four SDs in the first 14 patients, although final results are pending.

Farnesyltransferase inhibitors

Signal transduction from activated tyrosine kinases such as EGFR and PDGFR are mediated in part by the ras/raf/MAPK pathway (FIGURE 2). Activation of ras requires localization to the intracellular surface of the cellular membrane [147]. This subcellular localization is dependent on post-translational modification of the ras protein, catalyzed by the enzyme farnesyltransferase (FT), which results in the addition of a lipid hydrophobic farnesyl group to the carboxy-terminal. Specific inhibitors of FT (FTIs) have been generated to block the mitogenic function of ras. These inhibitors can also prevent the post-translational modification and function of many other farnesylated proteins. These include the centromere-associated proteins CENP-E and CENP-F, RhoB and -E, the nuclear lamins and Rap2. Two FTIs are currently being evaluated in malignant glioma, tipifarnib (R115777; Zarnestra®, Johnson & Johnson) and lonafarnib (SCH66336; Sarasar®, Schering-Plough). The NABTC recently completed a Phase I/II study of tipifarnib in recurrent malignant glioma. For patients receiving EIAEDs, the MTD is 400 mg/day with hydroxyurea (1000 mg/day) in the hope that hydroxyurea would improve CNS penetration of imatinib [146]. Preliminary results appear promising, with four PRs and four SDs in the first 14 patients, although final results are pending.

mTOR inhibitors

Activation of receptor tyrosine kinases such as EGFR, PDGFR and insulin-like growth factor (IGF) receptor result in increased signaling through the phosphatidylinositol 3-kinase (PI3K)/Akt pathway, as well as the MAPK pathway (FIGURE 2) [16,127,129,149]. Signaling through the PI3K/Akt pathway leads to activation by phosphorylation of a serine/threonine kinase, mammalian target of rapamycin (mTOR). mTOR plays a critical role in transducing proliferative signals mediated through the PI3K/Akt signaling pathway by activating the downstream protein kinase, p70 S6 kinase, and inhibiting the erythropoietic initiation factor 4E-binding protein (4E-BP)-1, which are required for ribosomal biosynthesis and translation of key messenger RNAs of proteins necessary for cell cycle progression from G1 to S phase [127,149]. In malignant gliomas there is increased signaling through this pathway as a result of overexpression of receptors such as EGFR or PDGFR, or deletion of PTEN, resulting in loss of inhibition of the PI3K/AKT pathway (FIGURE 2) [127]. Since mTOR plays a central role in this important pathway, there is significant interest in evaluating mTOR inhibitors as therapeutic agents in malignant glioma. Several mTOR inhibitors are undergoing evaluation, including sirolimus (rapamycin), temsirolimus (CCI-779), everolimus (RAD001) and AP23573.

Temsirolimus is an ester of the immunosuppressive agent sirolimus, which binds to the immunophilin FK-506 binding protein (FKBP)-12 and forms a complex which inhibits mTOR. In preclinical studies, temsirolimus has shown antitumor activity as a single agent, and in combination with cisplatin, in human medulloblastoma and malignant glioma cell lines [150]. Recently, the NABTC completed Phase I and II studies of temsirolimus in recurrent glioma [151,152]. In the Phase I study, the MTD of temsirolimus in patients receiving EIAEDs was 250 mg intravenously once weekly, and the dose for patients not on EIAEDs was 170 mg intravenously once weekly. Of the 29 patients evaluable for response in the Phase II study, there were two PRs (7%) and 12 SDs (41%) (FIGURE 4) [152]. However, the 6-month PFS was not prolonged. In a similar Phase II study of temsirolimus for patients with recurrent malignant glioma conducted by NCCTG, of 44 evaluable patients, three had minor responses and six had some reduction in the T2 signal abnormality around the tumor; there were no PRs [153]. These studies suggest that mTOR inhibitors have only very modest single-agent activity in malignant glioma.
VEGFR inhibitors

Inhibitors of VEGFR are potentially promising agents in malignant glioma, with the potential not only to inhibit angiogenesis, but also to decrease peritumoral edema [16]. The first VEGFR inhibitor to be used in malignant glioma, SU5416, was evaluated in a Phase I study by the NABTC. Although there were some patients who had SD with the drug, the study was discontinued when development of the drug was suspended. More recently, PTK787/ZK222584, a VEGFR and PDGFR inhibitor, was evaluated in a Phase I study in malignant glioma in combination with TMZ or lomustine [154]. Trials of other VEGFR inhibitors such as sorafenib (BAY 43–9006), AZD2171 and SU11248 are being planned.

Other potential targeted therapies

There are a large number of other potential targets for therapy in malignant glioma, such as IGF receptors, Raf, Mek, Akt, cell cycle components such as CDK4, and heat shock protein (HSP)-90. Other novel targets include histone deacetylases (HDACs), CXCR4 and cannabinoid receptors.

Histone proteins organize DNA into nucleosomes, which are regular repeating structures of chromatin [155]. The acetylation status of histones alters chromatin structure and is regulated by two classes of enzymes, HDACs and histone acetyltransferases (HATs) [155]. This acetylation affects the regulation of gene expression by rendering certain genes accessible to transcriptional machinery. There is increasing evidence that HDAC or HAT activity is altered in malignant glioma [155]. Inhibitors of HDAC can induce growth arrest, differentiation and/or apoptosis of tumor cells in vitro and in vivo by altering the transcription of a small number of genes [155] and represent a novel therapeutic approach. Several HDAC inhibitors such as depsipeptide (FK228) and suberoylanilide hydroxamic acid may enter clinical trials in malignant glioma in the near future. This class of drugs also potentially have synergistic activity with RT and chemotherapeutic agents.

The chemokine SDF-1α (CXCL12) acts through its receptor CXCR4 and has the capacity to influence proliferation and migration of neural precursor cells [156], raising the possibility that these molecules could potentially be therapeutic targets in CNS malignancies. CXCR4 is upregulated in GBM and inhibition of CXCR4 inhibits glioma growth in vitro and in vivo [156]. A variety of CXCR4 inhibitors are reaching clinical trials and may potentially have a role in malignant gliomas.

Malignant gliomas express cannabinoid receptors [157]. Administration of cannabinoids in glioma models results in apoptosis and significant antitumor effect [157,158]. Clinical trials using tetrahydrocannabinol are underway, although cannabinoids with more favorable pharmacologic properties will be necessary for the potential of this approach to be fully realized.

Summary & future directions

The first generation of studies of single-agent targeted molecular therapy have shown only modest benefit in malignant gliomas [16,126–132]. These results are similar to those seen with most other solid tumors. Many of the trials were conducted empirically without a clear understanding of the ability of these drugs to reach the tumors in adequate concentrations and inhibit the targeted receptors or signaling pathways in vivo. The challenge for the next generation of studies with these agents is to improve our understanding of the reasons for their success or failure, and to select the subgroups of patients who are most likely to respond to specific drugs. For example, it is likely that patients with PTEN deletions will respond best to mTOR inhibitors since the PI3K/Akt pathway is likely to be overactive in these patients (FIGURE 2). It is also becoming increasingly likely that single-agent activity will be modest. To increase the therapeutic benefit, it will be necessary to determine the most effective combinations of these agents with complementary targeted or conventional agents. Agents which target multiple receptors such as sorafenib (Raf kinase, VEGF and PDGFR inhibitors), PTK787/ZK222584 and SU11248 (VEGF and PDGFR inhibitors), AEE788 (EGFR and VEGF inhibitors) are also potentially attractive therapeutic agents for malignant glioma. Combinations of agents such as EGFR, FTI, or Raf kinase inhibitors, together or with mTOR inhibitors, also hold promise. Ultimately, the goal is to select the most effective combination of therapies based on the molecular phenotype of a patient’s tumor.

Although it is difficult to obtain tissue routinely in patients with glioma compared with hematologic malignancies and other systemic tumors, future trials incorporating more analyses of tumor specimens will be necessary [16,128,159]. Access to tissue will allow us to determine the ability of the drugs to penetrate into the tumor in therapeutic concentrations, their ability to inhibit the targeted receptors and signaling pathways in vivo, and the mechanisms by which the tumors remain resistant to the drug. This type of information will allow the rational design of future trials and hopefully result in more rapid development of effective therapies. Eventually, advances in neuroimaging may allow molecular genetic targets to be imaged noninvasively and reduce this need for tissue [160]. The design of clinical trials with this group of agents is also evolving. Traditional end points such as response are less appropriate to agents whose main benefit may be SD. Other end points such as time to tumor progression and 6-month PFS may be more appropriate. There is also a tremendous need for better surrogate markers of activity. In addition, much effort has been expanded in determining the MTD of specific agents in patients taking EIAEDs and non-EIAEDs. Drug development may be more efficient if initial studies are conducted in patients not on EIAEDs. If the drug is active, subsequent Phase I studies can be performed to determine the appropriate therapeutic dose in patients on EIAEDs. Although the first generation of studies with targeted molecular agents in malignant glioma have not shown the dramatic results seen with imatinib in CML and GIST, there is evidence of activity and this class of agents continues to hold tremendous potential.
Inhibition of angiogenesis

Glioblastomas are one of the most highly vascularized tumors in humans and represent an attractive target for inhibitors of angiogenesis [161–165]. One of the earlier studies of antiangiogenesis therapy in malignant glioma involved thalidomide, an inhibitor of VEGF and basic fibroblast growth factor (bFGF) [163]. Fine and coworkers conducted a Phase II study in which patients were initially treated with thalidomide 800 mg/day with increases in dose of 200 mg/day every 2 weeks until a final daily dose of 1200 mg was achieved [166]. The regimen was well tolerated except for fatigue and constipation. Of the 36 evaluable patients, there were two PRs (6%), two minor responses (6%) and 12 patients with SD (33%). Eight patients were alive more than 1 year after starting thalidomide, although almost all with tumor progression. Changes in serum levels of bFGF correlated with time to tumor progression and overall survival. Other studies using lower doses of thalidomide have shown similar evidence of modest benefit. Marx and coworkers treated patients with recurrent malignant glioma with thalidomide doses of up to 500 mg/day and obtained 5% PR and 42% SD [167], while Short and coworkers using only 100 mg/day of thalidomide found a 6% PR [168].

It is becoming increasingly clear that antiangiogenic agents alone have only modest antitumor activity and will probably have to be used in combination with other agents or RT to produce significant therapeutic effects. An example of this is a Phase II study by Fine and coworkers in which thalidomide was combined with carmustine in patients with predominantly recurrent GBM [169]. The objective response rate was 24%, and 24% of patients had SD (overall response of 48%). The 6-month PFS was 27%. These results compare favorably with historic data for carmustine alone. In contrast, a NABTC trial of TMZ combined with carmustine in patients with predominantly recurrent GBM [169]. The objective response rate was 24%, and 24% of patients had SD (overall response of 48%). The 6-month PFS was 27%. These results compare favorably with historic data for carmustine alone. In contrast, a NABTC trial of TMZ with carmustine did not prolong 6-month PFS [170].

A number of newer antiangiogenic agents such as Revlimid™ (CC-5013; an analog of thalidomide with increased antiangiogenic activity and fewer side effects), PTK787/ZK222584 (VEGF and PDGF inhibitor), sorafenib (Raf kinase, VEGF and PDGF inhibitor), LY 317615 (protein kinase C [PKC]-β2 inhibitor), cyclooxygenase (COX)-2 inhibitors, Col-3, endostatin, carboxamidotriazole, arsenic trioxide and celengitide (EMD121974; an inhibitor of αvβ3 and αvβ5 integrins) are currently undergoing evaluation in malignant glioma [162,163]. Other targeted molecular agents discussed above, such as imatinib and mTOR inhibitors, may also have antiangiogenic activity.

PKC-β2 is an important signaling molecule in the induction of, and signaling through the VEGF pathway, making it an attractive therapeutic target [171]. LY317615* disrupts the intrinsic phosphotransferase activity of conventional and novel PKC isoforms via an interaction at the ATP binding site and displays selectivity in inhibiting the β-isof orm. Preclinical studies demonstrated potent antiangiogenic activity of LY 317615. Promising activity has been seen in an ongoing Phase II trial of LY317615* in patients with recurrent malignant gliomas (five PRs in the first 28 patients) [171].

There is increasing evidence that COX-1 and -2 play an important role in cancer cell survival, growth and angiogenesis [172,173], suggesting that COX-2 inhibitors may have potential antitumor activity [169]. COX-2 expression is upregulated in glioma [174]. High COX-2 expression correlates with increasing histologic grade and is a strong predictor of poor survival [175]. Recently, there has been significant interest in using COX-2 inhibitors as a therapy for malignant glioma [176]. There are a large number of ongoing trials combining COX-2 inhibitors, such as celecoxib (Celebrex®, Pfizer), with cytotoxic and antiangiogenic agents. Apart from their antitumor effects, COX-2 inhibitors may also have a potential therapeutic role in treating peritumoral edema [177].

One potential limitation of antiangiogenic therapy is the possibility that while treatment may prevent enlargement of the tumor mass, tumor cells can still diffuse and infiltrate brain parenchyma [178]. It is likely that ultimately angiogenic inhibitors may be more effective when combined with cytotoxic therapies or drugs that inhibit invasion. Integrins αvβ3 and αvβ5 are critical components of angiogenesis. They are present on endothelial cells and promote invasion of endothelial cells into a wide variety of tissues, and maintain endothelial cell viability. Celengitide is a cyclic pentapeptide that targets the RGD sequence on vitronectin and acts as a specific inhibitor of both the αvβ3 and αvβ5 integrins, potentially inhibiting angiogenesis and invasion. Preclinical studies indicate that it has activity against malignant glioma [179,180], and clinical trials with this and similar agents are underway.

Antiangiogenic chemotherapy

There is increasing evidence that continuous low-dose chemotherapy (metronomic chemotherapy) may inhibit tumor-induced endothelial cell proliferation and prevent tumor growth [163,181]. Several trials using this approach are currently ongoing. In an interim analysis of one Phase II study of continuous low-dose etoposide alternating with cyclophosphamide, in combination with thalidomide and celecoxib in 39 heavily pretreated patients with malignant gliomas, the regimen was well tolerated. There was modest antitumor activity with 14% PR and 59% SD at their first scan in 6 weeks [182].

Differentiating agents

Retinoids

Retinoids are natural and synthetic compounds with diverse biologic effects against malignancies including growth inhibition, differentiation and angiogenesis inhibition. Preclinical studies have also shown that retinoids have growth inhibitory effects against gliomas, providing a rationale for the therapeutic use of these agents against malignant glioma [183].

13-cis-retinoic acid

13-cis is a synthetic analog to vitamin A that binds to retinoic acid and retinoid X receptors. It inhibits the growth and promotes differentiation of glioma cells in vitro [183]. The
precise mechanism of action is unclear but includes interference with EGF binding, inhibition of hepatocyte growth factor, inhibition of invasion and angiogenesis, promotion of apoptosis and modulation of antitumor immunity. In 1996, Yung and coworkers conducted a study of 13-CRA for recurrent gliomas and found modest activity (7% PR, 16% MR, 30% SD; MTP 16 weeks) [184]. In a more recent study of 85 GBM patients treated with 13-CRA (100 mg/m²/day in two divided doses for 21 days, followed by 7 drug-free days), there was 4% PR, 8% MR and 34% SD [185]. Progression-free and overall survival were 10 and 24.6 weeks, respectively. The 6-month PFS was 19%. These results suggest that 13-CRA has only very limited activity as a single agent. As previously noted, the combination of 13-CRA with TMZ appears to prolong 6-month PFS in patients with recurrent malignant glioma [66].

**Fenretinide**

Fenretinide (4-hydroxyphenyl retinamide) is a synthetic retinoid derivative that is more potent in inhibiting proliferation in human glioma cell lines than 13-CRA [185]. In a recently completed NABTC Phase II study of fenretinide at a dose of 600 mg/m² twice daily in patients with recurrent malignant gliomas, the drug was well tolerated but failed to prolong 6-month PFS [185]. Serum concentrations of fenretinide were low, suggesting that higher doses may be necessary to produce a therapeutic effect.

Studies combining retinoids with biologic, cytotoxic agents and RT are underway and may potentially result in increased antitumor effects. Other differentiating agents such as phenylacetate have not shown activity [186].

**Tamoxifen**

Tamoxifen is a PKC inhibitor with antiangioma effects in vitro [187]. In an early study of 11 patients with high doses of tamoxifen (80 mg twice daily in females and 100 mg twice daily in males) there were three PRs and one SD. Subsequent studies have confirmed a modest activity with this agent, especially in patients with AA [188]. In one study of 24 patients with AA, there was 17% PR and 46% SD. Tamoxifen has been combined with many other standard chemotherapeutic regimens without clear additional benefit to date.

IGF-1 is a thyroid hormone-modulated naturally occurring antagonist of tamoxifen-induced cytotoxicity. To improve upon the efficacy of tamoxifen, Herbergs and coworkers attempted to suppress thyroid function with propylthiouracil in 22 patients receiving high-dose tamoxifen [189]. Median survival was significantly longer in the 11 patients who became hypothyroid than in the euthyroid patients (10.1 vs. 3.1 months; p = 0.03). There was also a significant decrease in blood levels of IGF-1 (p = 0.02) in hypothyroid patients. Further studies will be needed to evaluate the value of this approach. IGF-1 inhibitors are entering clinical trials and potentially have synergistic effects not only with tamoxifen, but also many tyrosine kinase inhibitors.

**Gene therapy**

Malignant gliomas were one of the earliest neoplasms treated with gene therapy since they were localized tumors amenable to direct injection of viral vectors. Several reviews discuss the current status of gene therapy in detail [164,165,190–196]. The most commonly used strategy involves the administration of replication-incompetent retroviral and adenoviral vectors that transduce tumor cells with chemosensitization genes, increasing the sensitivity of the tumor cells to subsequently administered chemotherapeutic agents [190,197–200]. The earliest studies used viral vectors that transduced tumor cells with the herpes simplex thymidine kinase gene, sensitizing these cells to treatment with ganciclovir [197–200]. Other strategies involve the use of viral vectors to transduce tumor cells with tumor suppressor genes such as p53 [192,201], and to augment the antitumor immunity [202,203]. However, the initial enthusiasm for these approaches has been tempered by the limited results of the clinical trials to date. In general, these gene therapies have been well tolerated and there have been occasional patients who appear to have benefited [190,195,198,199]. However, the efficiency of transduction of tumor cells remains poor and significant obstacles remain [201]. Several reviews discuss the strategies that are currently being used to improve the effectiveness of this approach [192–196]. Recently, there has been increased interest in replication-competent viruses that discriminately target and replicate within tumor cells, destroying them while leaving adjacent postmitotic neurons relatively unharmed [191]. Herpes simplex virus (HSV)-1 mutants engineered to delete neurovirulence genes such as G207 and HSV1716 are completing Phase I studies and appear to be safe [191,204]. Second-generation replication-competent viruses containing chemosensitization genes are about to enter clinical trials. One example is MGH2, a herpes virus mutant containing both cytochrome P4502B4 to activate cyclophosphamide and carboxyl esterase to activate irinotecan [190]. Other oncolytic viruses being evaluated include ONYX-015 (a conditionally replicative adenovirus with E1B deletion that replicates in tumors cells with p53 mutations) [191], Newcastle disease virus (a paramyxovirus with increased replication efficiency in tumor cells) [191], revovirus (Reolysin; a RNA virus which replicates in tumors with upregulated Ras pathways) [191,205], attenuated polioviruses and vaccinia viruses [191].

**Immunotherapy**

Recently, there has been renewed interest in the use of immunotherapy for malignant glioma. However, progress remains limited [206–211]. The development of effective immunotherapies for malignant glioma is complicated by the relatively immunoprivileged environment of the brain, the paucity of well-characterized tumor-specific antigens, the production of immunosuppressive factors by malignant gliomas such as TGF-β, prostaglandin E2, IL-10 and a glioma-secreted soluble factor, as well as downregulation of major histocompatibility molecules on the tumor cell surface [210,211]. Early studies of adoptive immunotherapy with lymphokine-activated killer
cells and cytokine therapy with agents such as IL-2 and IFNs were largely ineffective and associated with significant toxicities [211]. In recent preclinical studies, neural stem cells (NSCs) secreting cytokines such as IL-4 appeared to exhibit tropism for malignant cells, raising the possibility that NSCs may be used as a form of targeted delivery of tumoricidal doses of cytokines to tumor cells [211].

The immunotherapeutic strategy that has been most extensively evaluated is the use of radiolabeled mAbs injected into the tumor cavity [38,39,212,213]. The best studied of these antibodies is a 131I-labeled murine antibody (81C6) that targets tenasin, an extracellular matrix glycoprotein, expressed ubiquitously in malignant gliomas [38,39]. In a Phase II trial of patients with newly diagnosed malignant gliomas, the 81C6 antibody was injected directly into the surgical cavity. These patients then received conventional RT and 1 year of chemotherapy. Median survival for all patients and those with GBM was 86.7 and 79.4 weeks, respectively. These results appear to be better than historic controls. 211At-labeled chimeric 81C6 antibodies, administered into surgically created resection cavities, are currently under evaluation in patients with recurrent malignant gliomas [38]. Astatine emits β-particles that have high energy transfer and cytotoxicity than β-emitters such as 131I. 90Y-labeled BC-4 antitenasin antibodies, which emit high-energy β-particles, have also been evaluated in patients with malignant gliomas [38,212]. These appear to be well tolerated and some long-term survivors were reported. In another strategy, the 125I-labeled mAb 425 directed against EGFR also appeared to increase survival when administered together with RT in patients with newly diagnosed malignant gliomas [213]. Although these mAbs appear to improve survival compared with historic controls, it is unclear what role selection bias played. One limitation of these mAbs is that their large size impedes diffusion through the tissues, reducing their ability to reach distant tumor cells. In an attempt to overcome this limitation, a strategy termed pretargeting has been developed in which glioma patients receive biotinylated BC-4 mAb, followed 24 h later by avidin, and then 18 h later a 90Y-labeled biotin conjugate [214]. A trial using this pretargeting approach was performed in recurrent glioma in which these reagents were administered into the tumor cavity. Median survival from reoperation for AA was 19 months and 11.5 months for GBM. A trial using this pretargeted immunotherapy strategy with a new antitenasin mAb, ST2146, is being planned [38].

There is also significant interest in a variety of vaccine strategies, especially dendritic cell vaccines made from patient’s own dendritic cells pulsed with tumor cell-surface peptides [206,208,211]. While some have shown augmentation of antitumor immunologic responses [215,216], and occasionally anecdotal reports of benefit [215], in general these approaches remain at an early stage of development. Other immunotherapeutic strategies being evaluated include peptide and DNA vaccines [211], vaccines transfected with IL-4 gene [217], and TGF-β antisense therapy [218].

Therapy for other malignant glioma

Glioblastomas, AA, AO and AOA account for the majority of patients with recurrent malignant glioma. Other malignant gliomas include gliosarcomas, anaplastic gangliogliomas, anaplastic ependymomas, astroblastomas and subsets of pleomorphic xanthoastrocytomas. Most of these are treated in the same manner as the more common malignant gliomas. Anaplastic ependymomas should be treated with reoperation or SRS/SRT if possible. Response to chemotherapy is generally poor, although there have been anecdotal reports of benefit from a variety of agents including carboplatin and TMZ [219–221].

Summary & conclusions

Although the prognosis of patients with recurrent malignant gliomas remains poor, there has been progress recently in developing more effective therapies. A number of studies have clarified the role of irinotecan for malignant glioma, and TMZ for AO and AOA. Results from the first generation of trials of targeted molecular agents have become available. In general, these agents are well tolerated, although single-agent activity is modest. Ultimately, truly effective therapies will result from the use of complementary combinations of targeted agents or the combination of targeted agents with other treatment modalities such as RT and chemotherapy. There is increasing interest in the administration of therapeutic agents into the tumor cavity or by convection-enhanced delivery. These include cytotoxic agents, mAbs, immunotoxins, radionuclides and viral vectors. Progress is also being made in the development of more effective gene therapies and immunotherapies.

Expert opinion

Recently, there have been important technologic advances in surgery and RT, increasing the safety of these therapies. Although both of these therapies have a role in patients with recurrent glioma, the infiltrative nature of these tumors makes it unlikely that local treatments will significantly improve prognosis. Only therapies that effectively treat both the infiltrating cells as well as the main tumor mass will prolong survival.

Conventional cytotoxic agents are the mainstay of treatment for recurrent malignant glioma, although to date they have had only a very modest impact. TMZ is the chemotherapy of choice for patients with recurrent malignant gliomas, if they have not received this drug previously. There is emerging evidence that the combination of TMZ and irinotecan [63], TMZ and CRA [66], and TMZ and cisplatin [69], may be more effective than TMZ alone. The combination of TMZ and EGFR inhibitors such as gefitinib [222] and erlotinib [138] are well tolerated, but their efficacy is unproven. The role of TMZ in recurrent malignant glioma is evolving. As TMZ becomes increasingly used with RT in newly diagnosed patients, its place in the treatment of recurrent disease is likely to diminish. This will also make it more difficult to study combinations of new biologic and targeted molecular agents in combination with TMZ in patients with recurrent tumors; many of these trials will have to be performed in the adjuvant setting. For patients who have already
Malignant gliomas are the most common form of primary brain tumors in adults, with an annual incidence of 5 per 100,000 people. Treatment options for recurrent malignant glioma are limited, with median time to tumor progression of only 9 weeks, and overall survival of approximately 4 months.

Surgery may have a limited role in symptomatic patients with tumors involving noneloquent areas and good performance status.

Brachytherapy, stereotactic radiosurgery and stereotactic radiotherapy are unproven methods of treatment in recurrent malignant glioma, although selected patients may benefit.

Temozolomide is the chemotherapy of choice for recurrent malignant glioma. In patients with glioblastoma, there is a 5% partial response (PR) rate and 40% stable disease (SD). The 6-month progression-free survival (PFS) is 21%. In patients with anaplastic gliomas, there is 8% complete response, 27% PR and 26% SD. The 6-month PFS is 46%.

Other chemotherapeutic agents with modest activity include carmustine, lomustine, procarbazine (PCV), irinotecan, carboplatin and etoposide.

Combinations of temozolomide with irinotecan, cis-retinoic acid or cisplatin may result in increased activity compared with temozolomide alone.

Anaplastic oligodendrogliomas and oligoastrocytomas are chemosensitive tumors, responding to PCV or temozolomide.

Anaplastic oligodendrogliomas with loss of 1p and 19q are particularly sensitive to both chemotherapy and radiation therapy and have a good prognosis.

Carmustine wafers implanted into the resection cavity increase median survival by approximately 2 months.

Intratumoral therapies undergoing evaluation include cytotoxic agents, radiolabeled monoclonal antibodies, recombinant fusion proteins of interleukin-13 and -4, or transforming growth factor-α with mutated forms of Pseudomonas exotoxin, and radiolabeled peptides derived from scorpion venom binding to chloride channels (125I-TM-601).

There is tremendous interest in targeted molecular therapies. Particular attention has focused on inhibition of epidermal growth factor, platelet-derived growth factor, vascular endothelial growth factor, the Ras/Raf/MAPK and the Akt/PI3K/mTOR pathways. The results of therapy with single agents have been modest, but studies combining targeted molecular agents with one another and with radiation therapy and conventional cytotoxic agents hold promise.

Antiangiogenic therapies with agents such as thalidomide have modest activity. A large number of novel agents and therapeutic strategies, such as antangiogenic (metronomic) chemotherapy, are undergoing evaluation. Ultimately, antiangiogenic agents may be most effective when combined with other modalities such as radiation therapy or chemotherapy.

Gene therapy with chemosensitization, immunostimulatory or tumor suppressor genes have produced only modest results, primarily as a result of the poor efficiency of transduction of tumor cells. There is also much interest in oncolytic viruses.

Immunotherapies have shown only limited benefit. Treatments under investigation include radiolabeled monoclonal antibodies, adoptive immunotherapy, dendritic cell vaccines and peptide vaccines.
Akt/PI3K/mTOR pathway. There is also significant interest in combinations of targeted agents with conventional cytotoxic drugs and RT.

There is renewed interest in the intratumoral therapies. These approaches bypass the blood–brain/tumor barrier and hold promise. The results of gene therapy and immunotherapy have been disappointing to date and additional studies are underway.

The treatment of patients with recurrent malignant gliomas continues to pose a difficult challenge. Nonetheless, there have been significant advances in our understanding of the biology of these tumors and an increasing number of promising therapies are being developed. It will be important to improve our pre-clinical ability to select the most effective agents or combination of agents for clinical development. Equally important will be the need for well-designed clinical trials with adequate correlative molecular, biologic and radiologic studies. These studies will help us not only to determine if a drug has activity, but also to understand the reasons for its efficacy or ineffectiveness, and ultimately enable subsets of patients who are most likely to benefit to be selected. The pace of research is accelerating and there is reason for optimism.

Five-year view

The success of rationally designed drugs and targeted molecular therapy has significantly improved outcome for patients with cancers such as CML and GIST. While the molecular changes in malignant gliomas are much more complex, there is the potential that similar progress can occur in the treatment of patients with malignant gliomas in the next few years. Advances in our understanding of the critical molecular changes driving growth in glioma, improved ability to molecularly profile tumors, improved transgenic animal models for preclinical testing of drugs, and the increasing number of novel therapeutic agents becoming available, improve the likelihood that important advances will occur. Ultimately, the goal is to be able to genotype each patient's tumor and allow the most appropriate therapeutic agents for each patient to be selected. The possibility of success is increased by the greater willingness of pharmaceutical companies to combine agents, and by the improved funding environment for translational research. There is also progress in developing novel intratumoral therapies and stem cell therapies, and improved gene therapies and immunotherapies. It is likely that over the next 5 years, some of these novel treatments will be effective and lead to increased survival and quality of life for patients with malignant gliomas.

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