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Recent advancements in multimodality treatment of gliomas

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Abstract

Gliomas account for the vast majority of malignant adult brain tumors. Even though tremendous effort has been made to optimize treatment of patients with high-grade glioma, the prognosis remains poor, especially for patients with glioblastoma. The dismal prognosis conferred by these tumors is in part caused by the tendency to diffusely infiltrate into neighboring brain tissue, but also by the inherent resistance of these tumors to both chemotherapy and radiation. This article reviews the recent advancements in multimodality treatment of patients with gliomas, both in the primary and recurrent setting, with an emphasis on the emerging targeted therapies. Moreover, the external beam radiotherapy options, including intensity modulated radiotherapy and particle (proton and carbon ion) radiotherapy are reviewed.

Keywords

glioblastoma; glioma; particle therapy; radiotherapy; targeted therapy

The incidence of primary malignant brain tumors has been increasing over the past 30 years, and it is estimated that in the year 2010, approximately 22,020 cases were diagnosed in the USA alone, with 13,140 deaths [201]. Gliomas account for 32% of all primary brain tumors, but within the malignant subset, they account for 80% of tumors. Histological classification of tumors of the nervous system was initiated by the WHO in 1979, as a means of predicting the biological behavior of a neoplasm, and thereby determining the choice of therapies [1]. According to the most recent classification (2007), malignant gliomas are classified into four WHO grades. Low grade gliomas (LGG), including grade I (pilocytic astrocytoma) and grade II oligodendroglioma, astrocytoma, and mixed oligoastrocytoma are relatively slow-growing neoplasms and account for approximately 10% of primary brain tumors. Cytological atypia alone defines the grade II tumor, and the best treatment approach for patients with these tumors is still unclear. Although the radiotherapy (RT) dose for patients

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with a grade II tumor is well-established, the timing of RT, precisely early versus delayed, remains contentious owing to the fact that potential toxicity must be balanced against the long natural survival.

High grade gliomas (HGG), including grade III anaplastic astrocytoma (AA), anaplastic oligodendroglioma (AO), anaplastic mixed oligoastrocytoma (MOA) and grade IV glioblastoma (GBM), account for approximately 60–75% of all gliomas. Histologically, tumors showing anaplasia and mitotic activity are classified as grade III, while the *sine qua non* of grade IV tumors is microvascular proliferation and/or necrosis. Historically, all HGG have been treated in the same manner, but the treatment modality for grade III tumors is currently being investigated separate of grade IV tumors through ongoing clinical trials. The average survival time of approximately 1 year for patients with glioblastoma (GBM) has minimally improved despite decades of basic and clinical research. However, in recent years a significant survival benefit has been achieved with the addition of concurrent temozolomide (TMZ) to adjuvant RT.

The dismal prognosis of GBM patients is in part caused by the resistance of these tumors to both chemotherapy and radiation, as most tumors recur within the irradiated portals. Poorly understood mechanisms of tumor resistance and migration account for such a high rate of recurrence and progression. Identifying the best treatment for each grade and molecular subtype of gliomas will help guide physicians in providing more effective therapies for patients. The current trends in cancer research aim to identify novel molecular targets for each glioma grade, and thereby enhance the therapeutic ratio of conventional and experimental therapeutics.

From the RT standpoint, the quest for optimizing local control of gliomas with external photon beam RT has evolved from the classic opposed lateral fields encompassing the whole brain to the highly conformal intensity modulated RT (IMRT). Other radiation modalities, such as particle RT, are also being investigated. In addition to reviewing the standard of care for different grade gliomas, we will also review the evolution of targeted therapy, as well as technological advances in neuroimaging and RT as part of treatment for these tumors.

Low grade gliomas

Low grade gliomas tend to exhibit a heterogeneous clinical behavior, and patients may survive from less than a year to 20 years or more after initial diagnosis [2]. In general, they are relatively slow-growing primary malignant brain tumors and majority are capable of undergoing higher-grade transformation. Standard treatment consists of surgical debulking whenever possible, so as to decrease the risk of recurrence and transformation to higher grade [3]. However, many aspects of treatment are controversial, namely timing and aggressiveness of surgery, as well as timing of RT and whether there is a role for chemotherapy. Controversy stems from the need to reconcile the risk of potential toxicities of aforementioned treatments in the relatively younger patient cohort, owing to the fact that LGGs have a long natural history. For older patients, the standard remains to proceed with immediate postoperative radiation. European Organization for Research and Treatment of Cancer (EORTC) and Medical Research Council (MRC) conducted a clinical trial wherein

311 patients with LGG were randomized after surgery to receive adjuvant radiation (54 Gy in 30 fractions) versus no adjuvant therapy until tumor progression, as defined by neurologic deterioration and/or radiologic progression [4]. After a median follow-up of 7.8 years, the irradiated group demonstrated a significant improvement in time to progression (TTP 5.3 vs 3.4 years, $p < 0.0001$), but not in median overall survival (mOS 7.4 vs 7.2 years). Of note, seizures were better controlled in the early RT group [5].

In general, patient presentation tends to dictate the initial course of treatment. Using distinct datasets from the EORTC trials with adult patients with LGG, Pignatti and colleagues have identified prognostic factors for survival in patients with LGG and derived a prognostic scoring system to help guide timing and aggressiveness of initial therapy [6]. Multivariate analysis identified the following five prognostic factors:

- Age (<40 vs ≥40 years)
- Largest diameter of the tumor (<6 cm or ≥6 cm)
- Tumor crossing the midline
- Histology type (oligodendroglioma, mixed glioma or astrocytoma)
- Presence or absence of neurologic deficit

The effect of each factor was considered to be one, and patients with two or fewer risk factors (i.e., low risk) were found to have an expected median survival of ≥7 years, whereas patients having three or more risk factors (i.e., high risk) have a significantly shorter median survival time. In the latter group, RT is recommended early or upfront after surgery, whereas in low-risk patients it is usually delayed until radiologic or symptomatic progression.

The North Central Cancer Treatment Group (NCCTG), Eastern Cooperative Oncology Group (ECOG) and the Radiation Therapy Oncology Group (RTOG) conducted a Phase III prospective randomized clinical trial of low versus high dose (50.4 Gy vs 64.8 Gy, delivered in 1.8 Gy fractions) RT in adults with supratentorial LGG, and after a median follow-up of 6 years, the 5 year disease-free survival (DFS) and OS were the same. The 2 year actuarial incidence of grade 3–5 radiation necrosis was double with the high-dose RT, 2.5 versus 5% [7]. Similarly, EORTC conducted a radiotherapeutic dose–response trial comparing adjuvant doses of 45 Gy versus 59.4 Gy in patients with LGG, and found no significant difference in terms of survival (58% for the low dose arm and 59% for the high-dose arm), nor the progression free survival (PFS 47 vs 50%) between the two arms of the trial [8].

Initial reports of effectiveness of chemotherapy in grade II glial tumors typically used the procarbazine, lomustine and vincristine (PCV) regimen, and more recently the effectiveness of adjuvant monotherapy with TMZ, an oral alkylating agent, has been tested in a trial setting, with reported response rates of 20–52% [9,10]. Results of the RTOG 9802 trial have been reported in abstract form and show that addition of PCV chemotherapy to adjuvant radiation in patients ≥40 years with suboptimal resection conferred a survival advantage beyond 2 years [11].

High grade gliomas

Historically, surgery followed by RT remained the gold standard treatment for HGG, but it conferred a dismal prognosis with an estimated 5 year OS of 2–3% [12]. Nevertheless, the effectiveness of postoperative radiation was so convincing in the early trials by the Brain Tumor Cooperative Group, that all subsequent trials of adjuvant therapy included radiation in all treatment arms. The efficacy of chemotherapy was more difficult to demonstrate, but most patients with HGG received additional carmustine or a combination regimen comprised of PCV [13]. However, the most recent paradigm shift in treatment of HGGs occurred with the EORTC Phase III study that demonstrated a significant survival benefit in patients with GBM with the addition of concurrent and adjuvant TMZ to radiation [14]. TMZ is a monofunctional alkylating agent, and has advantages such as ease of administration (*per os*), favorable toxicity profile, and the ability to cross the blood–brain barrier. In this landmark study by Stupp and colleagues, 573 patients with newly-diagnosed GBM (84% of which were surgically debulked) were randomized to receive RT alone (60 Gy in 30 fractions) or RT plus continuous daily TMZ (75 mg/m² body surface area from the first to the last day of RT), followed by six cycles of adjuvant TMZ (150–200 mg/m² body surface area for 5 days during each 28-day cycle) [14]. At a median follow-up of 28 months, the median survival was 14.6 months with RT plus TMZ versus 12.1 months with RT alone, rendering the hazard ratio for death 0.63 in the combined modality group. Moreover, the 2 year OS was 26.5% with RT and TMZ and 10.4% with RT alone. In this trial, patients whose tumor had a methylated methylguanine methyltransferase (*MGMT*) gene promoter had improved survival (mOS 21.7 vs 12.7 months, OS at 2 years 46 vs 13.8%) relative to those with an unmethylated *MGMT* promoter, and the methylation status was the strongest predictor for outcome and benefit from TMZ chemotherapy [15]. A 5-year analysis demonstrated that OS was 9.8% with RT and TMZ, versus 1.9% with RT alone [16]. Optimizing the adjuvant chemotherapy regimen is now one potential strategy to improve patient outcomes, specifically in patients with unmethylated *MGMT* promoter. A randomized Phase II trial that compared six cycles of adjuvant dose-dense (150 mg/m² days 1–7 and 15–21) or metronomic (50 mg/m² continuous daily) TMZ demonstrated that the former approach conferred a 1 year survival of 80%, median survival 17.1 months and PFS at 6 months of 56% [17].

Until recently, all HGGs have been treated in the same manner, but the treatment modality for AA, AO or anaplastic MOA tumors is currently being investigated separate of grade IV tumors through ongoing clinical trials. Accrual has completed for RTOG 9813, a Phase III randomized study of RT and TMZ versus RT and nitrosourea for AA and astrocytoma-dominant anaplastic MOA, and results are awaited.

Interest in the use of chemotherapy for patients with oligodendrogial or mixed gliomas was driven by the discovery that a subset of these patients exemplified remarkable chemosensitivity to the combination of PCV chemotherapy. EORTC conducted a randomized trial wherein 368 patients with AO or anaplastic MOA underwent resection and adjuvant RT alone with or without PCV chemotherapy. The 5-year analysis demonstrated that the addition of PCV chemotherapy improves PFS (RT + PCV 1.9 vs RT 1.1 years), but not OS (3.4 vs 2.6 years) in these patients [18]. Cairncross and colleagues demonstrated that

alterations of the chromosome arms 1p and 19q, in particular the loss of heterozygosity, confer chemotherapeutic sensitivity and prolong OS in grade III (anaplastic) AO treated with PCV [19,20]. In a series of 162 patients with pure or mixed glioma, Smith *et al.* demonstrated that the combined loss (deletion) of 1p and 19q is a statistically significant predictor of prolonged survival in patients with pure AO, independent of tumor grade [21]. No such association was demonstrated in patients with astrocytic neoplasms. All patients with the codeletion were alive after a median follow-up of 67.5 months, as opposed to 73% of those without the combined deletion. In this study, loss of 1p or 19q, in isolation, was not a significant predictor of OS in any of the subtypes examined, but patients with pure AO did demonstrate a trend ($p = 0.15$) toward better survival if their tumors exhibited loss of 1p or 19q.

In another series, 50 patients with AO were treated with a chemotherapeutic regimen (PCV in 48 patients) as the main initial adjuvant therapy, and patients with combined deletion of 1p and 19q had marked and durable responses to chemotherapy associated with long survival, with or without postoperative RT [22]. Patients with chromosome 1p alterations also responded superiorly to chemotherapy, but had shorter duration of response and survival. Tumors lacking 1p loss, but having a *TP53* gene mutation, responded to chemotherapy but recurred quickly. The group that fared the worst included tumors with intact 1p and wild-type *TP53*; these were poorly responsive, aggressive tumors that were clinically similar to GBMs. Within the subset of patients with AO who have the 1p/19q codeletion, those with polysomy of chromosomes 1 and 19 were found to have an earlier recurrence than those without polysomy [23].

Owing to a more favorable toxicity profile of TMZ compared with PCV, RTOG conducted a Phase II trial of preirradiation and concurrent TMZ in patients with newly diagnosed AO and mixed glioma. The objective response rate was 58% (32% complete response), and rate of progression during the pre-RT TMZ was only 10%, as compared with 20% in historical control with PCV [24]. All patients with codeletion of 1p/19q and/or *MGMT*-promoter methylation were free from progression at 6 months. Whether a chemotherapy-only regimen is sufficient to provide long-term control of 1p/19q codeleted AO or MOA without the use of concurrent or separate RT remains to be determined. EORTC is currently conducting CATNON, a Phase III intergroup trial on concurrent and adjuvant TMZ chemotherapy in patients with non-1p/19q deleted anaplastic glioma. The objectives of this trial are to assess whether concurrent RT with daily TMZ improves OS as compared with no daily TMZ in this patient population, and whether adjuvant TMZ improves OS as compared with no adjuvant TMZ. In addition, an intergroup trial by RTOG, EORTC and NCCTG is conducting the CODEL trial, wherein patients with 1p/19q codeleted WHO Grade III malignant gliomas will be randomized to one of three arms following maximum safe resection: RT, primary TMZ or RT and TMZ.

Targeted therapy in HGG

Recent discoveries in the field of molecular biology have identified several signaling pathways that are involved in the development of malignant behavior, as well as treatment resistance, of malignant gliomas. A better understanding of these molecular pathways has

allowed for development of so-called targeted therapy, which is considered an attractive therapeutic strategy to improve the prognosis of patients with HGG. One example of targeted therapy is EGFR tyrosine kinase inhibitors (TKI). *EGFR* overexpression has been demonstrated in malignant gliomas, and is associated with antiapoptotic tendency conferred by activated signaling pathways, tumor survival, and proliferation. Gefitinib and erlotinib are examples of EGFR TKIs that inactivate the downstream signaling pathways, and have been tested in the recurrent GBM setting [25]. However, clinical studies utilizing EGFR inhibitor monotherapy have shown disappointing results for recurrent GBM [26,27]. However, when used in combination with ionizing radiation the EGFR inhibitors have been shown to augment the antiproliferative and proapoptotic activity by ionizing radiation in several human cancer cell lines, as well as in mice bearing human colon cancer xenografts, as demonstrated by Bianco and colleagues [28].

RTOG conducted a Phase I/II study (0211) utilizing gefitinib with RT in patients with newly diagnosed GBM, and compared with historical studies, the combined therapy did not improve survival [29]. Prados and colleagues performed a Phase II study of combining erlotinib with RT and TMZ in patients with newly-diagnosed GBM, and demonstrated a 5 month improvement in the median survival with this approach (19.3 months vs 14.1 months in the combined historical control studies) [30]. In this study, a strong positive correlation between *MGMT* promoter methylation and survival was redemonstrated. However, other studies utilizing a similar approach of combined targeted and conventional therapy demonstrated inferior outcomes and high treatment-related toxicity and death rate [31,32]. The efficacy of EGFR inhibitors remains controversial for newly diagnosed GBM, although some patients have been reported to respond dramatically to EGFR inhibitor. To reconcile the disparity between EGFR overexpression in GBMs (up to 50% tumors) with only 10–20% of GBM patients that have a response to EGFR TKIs, biological markers to predict treatment response have been reported. Markers such as EGFR variant III (EGFRvIII), phosphatase and tensin homolog (PTEN) expression, and phospho-Akt (P-Akt), have been reported to predict the treatment response and can potentially be used to identify the patients that will derive survival benefit from the addition of EGFR inhibitor [33]. Specifically, coexpression of EGFRvIII and the tumor-suppressor protein PTEN was associated with a significant clinical response to EGFR TKI. Further studies are needed to discern the right type of patient with primary malignant brain tumor for EGFR inhibitor therapy, and how to optimize the therapeutic ratio with these agents in general. However, at least one other study did not corroborate the finding that the presence of EGFRvIII and intact PTEN predicts response to therapy with EGFR inhibitors [34,35].

In a recent Phase II multicenter trial of EGFRvIII-targeted vaccination in 18 patients with GBM who received the standard therapy of gross total resection followed by RT and concurrent TMZ, the 6 month PFS after vaccination was 67%, and median OS was 26 months [36]. The development of specific antibody or delayed-type hypersensitivity to EGFRvIII had a significant effect on OS. When these patients recurred, 82% had lost EGFRvIII expression.

Another class of targeted therapy includes antiangiogenic agents [37]. GBM has long been recognized as a highly angiogenic tumor. Bevacizumab, a humanized monoclonal antibody

that recognizes and blocks VEGF, was recently approved by the US FDA as a second-line or salvage treatment of GBM. Recent studies of recurrent GBM have shown that bevacizumab improved response rate and PFS, but specific adverse effects have also been reported, such as intracranial hemorrhage, gastrointestinal perforation, and thromboembolic complications [38,39]. To evaluate its effect in the upfront setting, Lai *et al.* conducted a Phase II study of bevacizumab and TMZ during and after RT for patients with newly diagnosed GBM [40]. They reported a median OS and PFS of 19.6 and 13.6 months, respectively. The authors concluded that the addition of bevacizumab improved progression-free survival, but not OS, compared with the historical studies. Currently, RTOG is conducting a Phase III double-blind placebo-controlled trial of conventional concurrent chemoradiation and adjuvant TMZ plus bevacizumab versus conventional concurrent chemoradiation and adjuvant TMZ in patients with newly diagnosed GBM. Results are impatiently awaited, as this study will determine the efficacy of adding bevacizumab to standard treatment.

Cilengitide, one of the other antiangiogenic drugs, inhibits $\alpha v\beta 3$ and $\alpha v\beta 5$ integrin receptors, resulting in apoptosis of GBM cells [41]. Cilengitide monotherapy for recurrent GBM has a modest effect and confers an approximate 6 month PFS of 15% [42]. Currently, Stupp and colleagues are conducting randomized studies of RT plus TMZ with or without cilengitide for newly diagnosed GBM, after showing in a Phase I/IIa study that addition of concomitant and adjuvant cilengitide to standard chemoradiotherapy demonstrated promising activity in patients with GBM with MGMT promoter methylation [43]. Initial results have been reported in abstract form and revealed a PFS at 6 months of 69%, PFS at 12 months 33%, and median PFS of 8 months. The OS at 12 months was 68%, and 35% at 24 months. In this trial, as well, both PFS (13.4 vs 3.4 months) and OS (23.2 months vs 13.1 months) were improved if *MGMT* promoter was methylated.

Multiple other targeted therapies combined with RT and TMZ have also been reported for malignant glioma, albeit most of them in the recurrent disease setting (Table 1). Targets include growth factor ligands, receptors, intracellular downstream effectors, as well as multitargeted kinase inhibitors (Table 1). Unfortunately, most of the reported results are not very encouraging. One of many targeted agents that have been tested is talampanel, a noncompetitive antagonist of the α -amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) receptor, which may inhibit invasion and growth of GBM [44]. In a multicenter Phase II trial of talampanel in addition to RT and TMZ for newly diagnosed GBM, median survival of 20.3 months and a 2 year OS of 41.7% was achieved. Of note, only 29% of patients in this series had MGMT promoter methylated, as compared with 43% in the EORTC study by Stupp [45]. Another agent that has been tested is bortezomib, a proteasome inhibitor that can arrest cell growth and induce apoptosis in GBM cells [46]. Phase I study of bortezomib with RT and TMZ in patients with primary and recurrent malignant gliomas demonstrated a median survival time of 15 months without severe toxicity [47].

These novel targeting therapies add to our armamentarium and enable us to devise a more effective treatment strategy by tackling the underpinnings of radioresistance of malignant gliomas. Although most studies are Phase I or II, with a relatively short follow-up time,

several of these agents warrant testing in a larger and randomized setting to truly discern their efficacy and safety, with the overarching hope of improving our patients' prognosis.

Imaging

Imaging of gliomas is of paramount importance for tumor delineation and design of local treatment (i.e., RT). LGGs show intact blood–brain barrier and typically lack contrast enhancement on computed tomography and MRI, thereby rendering them poorly demarcated and a challenge when it comes to tumor delineation [48]. PET has been used to assess cerebral metabolism of patients with gliomas, but the ^{18}F -2-fluoro-2-deoxy-D-glucose (FDG) tracer has not been accepted as a tracer of choice for patients with brain tumors, because of the high uptake by normal gray matter, thereby limiting the tumor recognition capacity. Taking advantage of tumor cells' increased expression of amino acid transporters, radiolabeled amino acid tracers have demonstrated increased sensitivity and specificity as compared with computed tomography, MRI and FDG-PET in diagnosis of glial brain tumors. L-methyl-(^{11}C)methionine (MET) tracer has been shown to have a relatively low uptake by brain parenchyma, but high uptake of the amino acid tracer by tumor cells. Owing to this, MET-PET has largely supplanted the FDG-PET in assessing the extent of glial tumors of all grades [49]. Moreover, it can be used to differentiate between recurrent brain tumors and radiation necrosis, as well as to aid in target delineation in RT planning [50]. However, owing to the short physical half-life (20 min) of carbon-11, on-site cyclotron is necessary for MET-PET examinations. To obviate this need, another amino acid tracer with comparable quality to MET-PET is O-(2-(^{18}F)fluoroethyl)-L-tyrosine (^{18}F -FET) tracer, with a half-life 110 mins. It is increasingly used in a diagnostic and treatment planning capacity [51].

Intensity modulated radiation therapy

Radiotherapy has improved several clinical end points in brain tumors, including OS in GBM and PFS in LGG [52]. For decades, it has remained the standard adjuvant treatment for HGGs, and is the primary treatment modality for unresectable HGGs. However, RT can also substantially contribute to late tissue toxicities such as radionecrosis and neurocognitive dysfunction, as per dose–volume relationship that dictates the risk of toxicity. Therefore, the therapeutic challenge in the use of external beam RT for brain tumors is establishing a balance between tumor control and the normal tissue tolerance. Given that most recurrences are local and that the outcome with partial brain RT is not inferior in terms of tumor control or OS, the field arrangement for gliomas has evolved from opposed lateral fields encompassing the whole brain to conformal RT, and has now culminated with IMRT. With the advent of computed tomography, 3D conformal RT (3DCRT) has become widespread in its use for nearly all treatment sites, including brain, because of its advantages in improving conformity of dose around the target. IMRT is one form of 3DCRT that is optimized to protect adjacent normal tissues from high doses of radiation while still delivering adequate doses to the target volume. Although conventional 3DCRT can achieve similar results, the dose fall-off at the edge of the treatment volume with IMRT can be much more pronounced when compared with that of conventional 3DCRT, which is important especially when the treatment volume abuts an important structure. In the brain, achieving dose reductions in the

normal tissues such as brain stem and optic apparatus translates into more favorable toxicity profile. The basis of IMRT is the inverse-planning system, which optimizes delivery of nonuniform beam fluences from multiple directions, and involves the use of multileaf collimators that divide each beam into many small beamlets of varying intensity [53]. In terms of local control afforded by IMRT for gliomas, it is comparable to that of conventional 3DCRT. Theoretical concern with the use of IMRT is that it can increase the normal tissue integral dose (NTID), which is the volume integral of the dose deposited in a patient. This is said to be owing to larger number of monitor units used in IMRT, and the concern is that the volume of normal brain exposed to any dose of radiation can increase the risk of secondary brain tumors [54]. To minimize this risk, it has been demonstrated that NTID is a function of beam energy and number of beams, and with four to eight or more beams, the variation in NTID is 1% [55].

Reirradiation of patients with glioma

Local recurrence remains the most common form of relapse in patients with HGG [34]. Currently, the salvage options include resection, systemic agents and reirradiation. Increasingly, stereotactic radiosurgery (SRS) and (hypo)fractionated stereotactic RT (SRT) are being used in patients with recurrent HGG, especially if surgical extirpation is not an option. Both approaches utilize modern, sophisticated RT modalities that allow for delivery of very conformal high dose radiation. Fogh and colleagues have reported the largest series to examine the efficacy and tolerability of hypofractionated SRT (H-SRT). They treated 147 patients with recurrent HGG who were treated with a median dose of 35 Gy in 3.5 Gy fractions [56]. In this series, H-SRT was administered independent of reoperation or concomitant chemotherapy. This treatment was well tolerated and resulted in a median survival time of 11 months. In another relatively large series, 101 patients with recurrent HGG were treated with fractionated SRT to a median dose of 36 Gy in 2 Gy fractions (5×2 Gy per week) [57]. Treatment was well-tolerated and effective, with a median survival after reirradiation of 8 months for patients with GBM, and 16 months for patients with WHO grade III tumors. The same median survival time was reported by the same group for patients who received reirradiation with fractionated SRT in combination with temozolomide [58]. Cuneo *et al.* treated 63 patients with recurrent HGG (49/63 GBM) with stereotactic radiosurgery and adjuvant bevacizumab, and median PFS and OS from SRS were 6 and 10 months, respectively [59]. The 1 year OS from SRS for patients with GBM who received bevacizumab was 50 versus 22% for patients not receiving adjuvant bevacizumab.

Given the increasing number of institutional series examining the safety and efficacy of reirradiation of patients with recurrent HGG, a prospective study corroborating the aforementioned results would likely effect a paradigm shift in how patients with recurrent disease are treated.

Particle therapy

Particle therapy, such as proton and carbon ion RT, has an inherent physical advantage, the so-called Bragg peak, which allows for increase in energy deposition at the end of beam's

path [60]. Favorable dose distribution with these modalities is achieved by 'spreading' the Bragg peak to ensure tumor volume coverage, but allowing for a steep dose fall-off at the field borders, which implies more sparing of organs at risks compared with photon therapy. Therefore, particle therapy is being considered as an attractive modality for glioma patients, because it may allow for delivery of higher dose of radiation to the tumor, but with reduced toxicity to surrounding normal tissues. Protons and carbon ions have a higher linear energy transfer than photons, a measure of particle's ability to induce DNA damage per unit length, although relative biologic effectiveness of protons is similar to that of photons [61]. By contrast, carbon ions have a higher relative biologic effectiveness compared with protons. This biological advantage leads to greater degree of irreparable DNA damage. In addition, the radiation effects of these modalities are less dependent on oxygen concentration in tumor, and thereby more effective against the hypoxic tumor cells [62,63].

Clinical studies of proton therapy have been performed for several types of tumors, including gliomas [64]. Fitzek *et al.* conducted a Phase II study of 23 GBM patients treated with radiation dose-equivalent of 90 Gy equivalent (GyE) utilizing protons and photons [65]. The median survival was 20 months, although most patients experienced radiation necrosis within high radiation dose area. Recently Mizumoto *et al.* conducted a Phase I/II study of 20 GBM patients treated with hyperfractionated concomitant boost proton therapy (96.6 GyE in 56 fractions) [66]. The 2 year OS was 45.3% and median survival time was 21.6 months. They concluded that this treatment was tolerable and beneficial. Fitzek *et al.* used a similar approach on patients with grade 2 and 3 gliomas treated by dose-escalation with proton and photon therapy (68.2–79.7 GyE) [67]. However, this study failed to improve outcome compared with historical studies. Hug *et al.* reported on 27 pediatric LGGs treated with proton therapy (50.4–63.0 GyE) [68]. The authors suggested that proton therapy was effective and safe for these patients. Given these findings in relatively small cohorts, proton therapy for glioma patients appears to have at least as favorable an outcome as photons and is well tolerated, but the rates of radiation necrosis are higher. In order to discern whether a meaningful difference in patient outcomes exists, a direct comparison between proton and photon therapies for glioma patients needs to be explored. Further studies are warranted to establish the efficacy and safety of proton therapy for glioma patients.

Theoretically, carbon ion therapy is also expected to improve the prognosis in glioma patients, owing to its physiological and biological advantages. Preclinical study demonstrated that carbon ion is more effective in killing GBM cells compared with photons [69]. Mizoe *et al.* conducted a Phase I/II studies of carbon ion therapy for 48 patients with malignant gliomas [70]. This study applied carbon ions as a boost therapy (16.8–24.8 GyE) following 50 Gy of photon therapy with nimustine hydrochloride. Median survival times of anaplastic glioma and GBM were 35 and 17 months, respectively. High carbon dose group (24.8 GyE) had better OS, and toxicity was generally low. Concurrent and adjuvant TMZ plus photon therapy is the standard treatment for GBM, but the efficacy of adding TMZ to carbon ion therapy has not yet been demonstrated in clinical study. *In vitro* studies suggest that carbon ion and TMZ synergistically decrease survival in GBM cells [71]. Combs *et al.* are conducting a randomized Phase II study in patients with GBM, comparing carbon ion therapy (18 GyE in 6 fractions) with proton therapy (10 GyE in 5 fractions) as a boost

following 50 Gy of photon therapy with concurrent TMZ [72]. In the near future, this study will show the efficacy of particle therapies with TMZ for GBM patients.

Although particle therapies were previously available in only a handful institutions, proton therapy is currently offered in tens of centers worldwide, including nine in the USA, while the carbon ion therapy is currently available in Japan and Germany [73]. Having increased access to particle therapy will enable investigators to perform more clinical studies in the future, and help answer the question of their relative efficacy against glial and other tumors.

Future perspective

As we learn more about cellular pathways and effectors involved in gliomagenesis, there will likely be a paradigm shift from the uniform standard-of-care treatment for all patients to a more individualized treatment based on molecular biomarkers. The aforementioned targeted therapies will help us devise a more effective treatment strategy by tackling the underpinnings of resistance of malignant gliomas. The challenge before the scientific and clinical community will be to identify the key targets and formulate therapy accordingly. Foregoing the 'one-size-fits-all' approach will lessen the harm done to the patients, as we know from the clinical trials that both standard and novel therapies may cause serious toxicities. Several of the newer agents warrant testing in a larger and randomized setting to truly discern their efficacy and safety, with the overarching hope of improving our patients' prognosis. The most recent update from Stupp and colleagues regarding integrin inhibition with addition of cilengitide to standard chemoradiotherapy shows promise to potentially become the new standard-of-care for patients with GBM, suggesting that the most effective strategy is to target both the extracellular (e.g., integrin) and intracellular effectors. Moreover, just as the methylation status of the *MGMT* promoter did, greater characterization of gene expression by epigenetic regulation may help us elucidate additional mechanisms of resistance or sensitivity to therapy.

In summary, gaining a better understanding of the molecular brain tumor population(s) that benefit from each targeted therapy will lead to more effective personalized therapy. It is hoped that a more targeted therapeutic approach will overcome the current limitations in the treatment of patients with malignant gliomas and result in a better prognosis for patients with brain tumors.

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Executive summary

Incidence of brain gliomas is increasing

- Oligodendrocytic histology portends better survival compared with astrocytic histology, especially if 1p 19q deleted.
- Marginal improvement in survival of patients with high grade gliocytoma owing to complex mechanisms of tumor resistance and migration.
- Standard of care treatment for high-grade gliocytoma is maximum safe resection, followed by chemoradiotherapy and maintenance temozolomide.
- Patients with methylated *MGMT* promoter have a better prognosis.
- Optimizing adjuvant systemic therapy regimen is a potential strategy to improve outcomes in patients with unmethylated *MGMT* promoter.

Targeted therapy against several glioma signaling pathways may improve survival

- Addition of anti-VEGF and anti-integrin therapy to standard of care treatment currently tested in Phase III trial.
- Targeted therapy currently explored in clinical trials aims at both intra- and extra-cellular targets.

Imaging of gliomas cannot always discern radiation-induced tumor necrosis from tumor progression

- Radiolabeled amino acid tracers have increased sensitivity and specificity in diagnosing gliomas, as well as progression versus treatment-related effect.
- Methionine tracer has high uptake by tumor cells, as does O-(2-[18F]fluoroethyl)-L-tyrosine tracer (18F-FET).
- MET- and 18F-FET PET are increasingly used in a diagnostic and treatment planning capacity.

Intensity modulated radiotherapy is the most sophisticated way of delivering radiotherapy to gliomas

- Intensity modulated radiotherapy is optimized to protect adjacent brain parenchyma from high doses of radiotherapy while delivering adequate doses to the target area.
- The dose fall-off at the edge of treatment volume is more pronounced than with conventional three-dimensional conformal RT.

Particle therapy currently tested in a limited number of centers

- Particle therapy has higher relative biological effectiveness, imparting a greater degree of irreparable DNA damage.
- Proton and carbon ion radiotherapy has the so-called Bragg peak, allowing for increase in energy deposition at the end of the beam's path.

- More sparing of unaffected organs/tissue at risk compared with photon therapy.
- May allow for delivery of higher dose of radiation to the tumor, with reduced toxicity to surrounding tissue.

Conclusion

- Better understanding of pathways involved in gliomagenesis, invasion and treatment resistance will allow for better targeting.
- Greater characterization of epigenetic regulation may help elucidate additional mechanisms of resistance or sensitivity to therapy.
- The challenge before the scientific and clinical community will be to identify the key targets and formulate therapy accordingly, thereby foregoing the 'one-size-fits-all' approach.
- Identifying the patient subsets that benefit from different targeted therapy will lead to more effective personalized therapy.

Table 1

Recent clinical trials with targeted therapy.

Targets	Agents	Patient	Phase	Results	Ref.
Growth factor ligands					
VEGF	BEV + RT + TMZ → TMZ + BEV	New Dx	II	OS 19.6 months PFS 13.6 months vs 21.1 and 7.6 months in control cohort, and vs 14.6 and 6.9 months in EORTC cohort	[40]
VEGF	BEV + RT + TMZ → TMZ + BEV	New Dx	III	mPFS 17 months (vs 7 months without BEV) mOS not reached (17 months without BEV)	[74]
VEGF	BEV + irinotecan	Recurrent	II	PFS at 6 months 37%	[75]
VEGF	BEV + fotemustine	Recurrent	II	Overall response 35% mTTP 2.6 month 15/31 FFP (2–8 months)	[76]
VEGF	BEV q 3 weeks	Recurrent	II	PFS at 6 months 32%, mPFS 3.9 months, mOS 6.6 months; CR 0%; PR 25%; SD 50%	[77]
VEGF, vascularity	BEV + fosbretabulin	Recurrent	I	Pilot study outline only reported	[78]
TGF-β 2	Trabectedin	Recurrent	IIb	AA: OS 24 months 83% with lower dose GBM; mOS 17.4 month Phase III started	[79]
Growth factor receptors					
pan-VEGFR	Cediranib + RT + TMZ	New Dx	Ib	MTD reached. 6/6 patients alive at 156 days median follow-up. Phase II underway	[80]
pan-VEGFR	Vatalanib + RT + TMZ	New Dx	I/II	MTD reached. Phase II discontinued owing to industry decision not to further develop agent	[81]
pan-VEGFR	Cediranib	Recurrent	II	56.7% radiologic response, PFS-6 25.8%, manageable toxicity. Biomarkers associated with response and survival	[82]
VEGFR-2	CT-322	Recurrent	II	MTD reached. Clinically active. PFS-6 with CT-322 alone 21.4%, with CT-322 plus irinotecan 57.1%	[83]
VEGFR	RT + TMZ → TMZ + sorafenib	New Dx		Median PFS 6 months; PFS at 1 year 16%. Median OS 12 months. 40% patients did not receive maintenance sorafenib	[84]
VEGFR	Sunitinib + irinotecan	Recurrent	I	MTD reached, SD 73%	[85]
VEGFR	Sunitinib	Recurrent	II	mTTP 1.6 months, mOS 3.8 months	[86]
PDGFR-β	Tandutinib	Recurrent	I	MTD achieved. Phase II initiated	[87]
Intracellular effectors					
PKC-β and PI3K/Akt pathway	Enzastaurin vs lomustine	Recurrent	III	n = 266; OS 6.6 vs 7.1 months, median PFS 1.5 vs 1.6 months. No superior efficacy compared with lomustine, but better hematologic toxicity	[88]
PKC-β and PI3K/Akt pathway	Enzastaurin + RT + TMZ	New Dx	II	24/60 PD, OS, PFS will be reported	[89]
mTOR	Temsirolimus + RT + TMZ	New Dx	I	MTD established. Increased risk of opportunistic infections	[90]
mTOR	RAD001 + TMZ (maintenance)	New Dx	I	MTD reached	[91]

Targets	Agents	Patient	Phase	Results	Ref.
bcl-2	R(-)-gossypol	Recurrent	II	OS pending. PR: 1/43; SD: 7/43	[92]
VEGFR, PDGFR, RAF	TMZ + sorafenib (maintenance)	New Dx	II	CR: 1%; PR: 11%; SD: 49%; PD: 31% mPFS 6 months; mOS 16 months	[93]
RAS (farnesyl transferase)	SCH 66336 + TMZ	Recurrent	I	MTD reached. 2 PR, 14 SD, 11 PD	[94]
VEGF, histone de-acetylase	Vorinostat + BEV + irinotecan	Recurrent	I	Currently enrolling at the dose level 3 vorinostat, with planned follow-up Phase II trial	[95]
PARP-1	BSI-201	New Dx	I	MTD not reached with TMZ, encouraging safety profile	[96]
Multitargeted kinase inhibitors					
VEGF, EGFR	BEV + erlotinib	Recurrent	II	PFS-6 28% (GBM) and 44% (AA); mOS 42 weeks (GBM) and 71 weeks (AA)	[97]
VEGFR, EGFR	Vandetanib + RT + TMZ	New Dx	I	MTD reached. DLTs included GI hemorrhage, GI perforation and cytopenias. Phase II under way	[98]
VEGFR, EGFR	Vandetanib + etoposide	Recurrent	I	MTD not reached. Patients remaining stable in study	[99]
VEGFR, EGFR, PDGFR	Vandetanib + imatinib + hydroxyurea	Recurrent	I	MTD reached. PR: 1/16; SD: 15/16 for at least 4 weeks	[100]
VEGFR-2, EGFR	Vandetanib	Recurrent	I/II	MTD reached; median PFS-6: 1.8 months, mOS: 7.4 months	[101]
VEGFR, EGFR	BEV + cetuximab + irinotecan	Recurrent	II	Radiographic response: 34%. PFS-6 30%. 3/32 patients with DVT. Efficacy not superior compared with BEV + irinotecan alone	[102]
EGFR, mTOR	Erlotinib + temsirolimus	Recurrent	I/II	MTD reached. PR: none; SD: 30%; PFS-6: 12.5%	[103]
EGFR, mTOR	Erlotinib + sirolimus	Recurrent	II	47% with SD, no patients with PR or CR. PFS-6 3.1%. PFS better for patients not on EIAEDs (p = 0.03)	[104]
EGFR, VEGFR	Erlotinib + sorafenib	Recurrent	I/II	MTD reached. Outcome data pending	[105]
VEGFR, mTOR	Sorafenib + temsirolimus	Recurrent	I/II	MTD reached. PFS-6 0%	[106]
MET, RET, VEGFR2	XL184	Recurrent	II	38% had >50% tumor reduction (PR), 35% between +24% and -49% enhancement, 27% >25% PD	[107]
MET, RET, VEGFR2	XL184	Progressive	II	PFS-6: 21%; ORR: 21% (AAT naive) vs 8% (prior AAT); mean duration of response 5.9 months	[108]
VEGFR, PDGFR, KIT, EGFR, HER-2	Pazopanib + lapatinib	Recurrent	I/II	MTD reached. Phase I: PR: 3%; SD: 18%; Phase II: PR: 1/2; CR: 1/2	[109]
Miscellaneous					
Integrins	Cilentide + RT + TMZ → RT + TMZ	New Dx	I/IIa	PFS-6: 69%; PFS-12: 33%; OS-12: 68%; OS-24: 35%. PFS and OS longer if MGMT promoter methylated	[43]
Selective integrins	Cilengitide	Recurrent	IIa	OS at all time points significantly higher with 2 g dose vs 0.5 g dose	[110]
LDL receptor-related protein	ANG1005	Recurrent	I	MTD reached; SD in 56% patients. Median time to progression in responders 23.9 weeks	[111]
CDK/TRKA	PHA-848125	Recurrent	I	MTD reached; transaminase elevation dose limiting	[112]

AA: Anaplastic astrocytoma; BEV: Bevacizumab; CDK: Cyclin-dependent kinase; CR: Complete response; DLT: Dose limiting toxicity; DVT: Deep venous thrombosis; Dx: Diagnosis; GBM: Glioblastoma; GI: Gastrointestinal; LDL: Low density lipoprotein; MGMT: Methylated methylguanine methyltransferase; mOS: Median overall survival; mPFS: Median progression free survival; MTD:

Maximum tolerated dose; mTTP: Medium time to progression; OS: Overall survival; PD: Progressive disease; PFS: Progression free survival; PR: Partial response; q: Every; RT: Radiation therapy; SD: Stable disease; TMZ: Temozolomide. Data taken from [202].