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Medical therapy of gliomas

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Abstract

Medical therapies are an important part of adjunctive therapy for gliomas. In this chapter we will review the chemotherapeutic and targeted agents that have been evaluated in clinical trials in grade II–IV gliomas in the last decade. A number of randomized phase III trials were completed and reported. There has been a clear success in oligodendroglial tumors and low grade glioma. Although some progress has been made in glioblastoma, considerable work involving the multidisciplinary collaboration of basic science, translational and clinical investigators needs to be done to improve the outcome of patients with anaplastic astrocytoma and glioblastoma. In addition, tailoring treatment based on molecular cytogenetic characteristics is a major focus of research into precision based medicine for glioma.

Keywords

Chemotherapy; Targeted treatment; Gliomas; Glioblastoma; Clinical trial; Molecular profile; Multidisciplinary

Introduction

The challenges that limit the therapeutic efficacy of chemotherapy and targeted therapies in gliomas include the blood–brain barrier (BBB), active transport mechanisms of drug efflux, and high plasma protein binding of agents [1]. In addition to the difficulty of delivery of agents across the BBB, there are other challenges that limit the efficacy of these agents. Other challenges include heterogeneity of tumors, redundancy of pathway interactions, lack of accurate and reproducible biomarkers to select patients for specific therapies, and difficulty in assessing target modulation [2–4]. Intrinsic and rapidly acquired resistance further limit the efficacy of chemotherapy or targeted therapy. Chemotherapeutic approaches

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have demonstrated efficacy in oligodendroglioma. For several chemotherapy-refractory tumor types including glioblastoma and anaplastic astrocytoma, new approaches continue to be explored and will be reviewed. Finally, the future directions involving precision medicine approaches to optimize the therapeutic index of drug treatments for glioma will be discussed.

Low grade gliomas (WHO grade II)

Until recently, low-grade gliomas were considered to be chemotherapy resistant and there have been limited trials evaluating the utility of chemotherapy in low-grade glioma in adults. In a small Southwest Oncology Group trial, patients with incompletely excised low-grade gliomas were randomized to radiation therapy (RT) alone or combination of RT and lomustine (CCNU). The survival in both the two arms was similar [5]. Radiation Therapy Oncology Group (RTOG) study, RTOG-9802 examined the role of adjuvant chemotherapy —procarbazine, CCNU, and vincristine (PCV) for “high-risk” adults (less than total resection, age older than 40 years) with low-grade gliomas. Two hundred and fifty-one patients were randomized to RT alone or RT followed by six cycles of PCV. Progression-free survival (PFS) but not overall survival (OS) was improved in the RT and the PCV group compared to RT alone at the time of the initial data analysis [6]. At the time of that report however 65 % of the patients were still alive. A recent National Institute of Health press release on more mature results of this study reported significant improvement in OS in the PCV chemotherapy plus RT arm (13.3 years) compared to those assigned to RT alone (7.8 years) at a median follow-up of 12 years [7]. Correlative studies to establish the predictive role of molecular and cytogenetic characteristics [isocitrate dehydrogenase (IDH) mutations, loss of heterozygosity of 1p/19q, as well as methylation of methylguanine methyl transferase (MGMT) status] clinical outcome are pending.

The first results from the RTOG 0424 study demonstrated the improved 3-year OS of a regimen of concurrent and adjuvant temozolomide (TMZ) and radiotherapy in a high-risk low-grade glioma population compared to the 3 year OS rate of the high risk EORTC LGG patients reported by Pignatti et al. [8]. The 3 year OS rate was 73.1 % (95 % CI 65.3–80.8 %), significantly improved in comparison to the pre-specified historical control (*p* value <0.0001) [9]. There is an ongoing intergroup phase III trial to address the role of adjunctive TMZ for LGG.

Several studies have evaluated PCV and TMZ in recurrent low grade gliomas [10–21]. Approximately half the patients treated with either TMZ or PCV experienced imaging stability or improvement of neurologic symptoms in these studies. The limitations of these studies include small numbers and the varied imaging criteria used to assess response. Patients with low-grade oligodendroglial tumors with 1p/19q deletion or t(1p; 19q) have longer PFS and OS than those without [22] and consequently, 1p/19q determination is important in stratification in future clinical trials. A randomized phase III EORTC trial stratified patients with low-grade glioma by 1p status prior to randomization to RT versus TMZ alone [23]. In the first report of the trial, PFS was similar in both groups while median OS was not reached. This study showed 1p deletion as a positive prognostic factor

irrespective of treatment at the time of this first analysis [PFS 0.0003; HR 0.59, 95 % CI (0.45–0.78); OS 0.002; HR 0.49, 95 % CI (0.32–0.77)].

Recent studies have identified alterations in the BRAF serine/threonine kinase gene as the likely causative mutation in childhood LGG and approaches to target this abnormality are being explored [24]. In addition, aberrant signaling in pathways including the phosphatidyl inositol-3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) network [25, 26] have also been identified in LGG and clinical trials are currently ongoing to target this pathway as a therapeutic approach.

In addition to the known side effects of myelosuppression from the use of alkylating agents, there may be adverse effects on the mutational landscape of tumors following this known mutagenic treatment. Johnson et al. [27] reported on a group of patients with grade II astrocytoma for whom tumor tissue was available for genomic analysis at the time of initial diagnosis and at the time of progression. They demonstrated the potential for TMZ to induce specific driver mutations that could contribute to the malignant transformation of grade II astrocytoma to glioblastoma. It is unclear which subset of patients is at specific risk for this mutagenic effect of TMZ.

Anaplastic oligodendrogliomas (WHO grade III)

Several retrospective series and phase II trials suggested chemosensitivity of oligodendrogliomas [12, 28, 29]. Two randomized prospective phase III trials evaluated the role of chemotherapy in this tumor type and patients were treated with either RT alone or RT in combination with PCV. In the RTOG-9402 trial, patients were randomized to either four cycles of intensified PCV followed by RT or immediate RT without chemotherapy. At initial report, survival in the two groups was the same and patients with 1p/19q deletions had significantly better outcomes, regardless of type of treatment [30]. A posthoc analysis showed that there was a PFS benefit from PCV that was most notable in patients with 1p/19q deletions. With over 11 years follow-up, mature data from this study showed that median survival of those with co-deleted tumors treated with PCV plus RT was twice that of patients receiving RT (14.7 vs. 7.3 years) [31]. The survival of patients with co-deleted tumors was better than those with non-co-deleted tumors regardless of treatment. The survival was not statistically significant for patients with tumors lacking 1p/19q deletion irrespective of treatment (median survival 2.6 vs. 2.7 years).

In the EORTC 26951 trial, 368 patients received immediate RT only or RT followed by six cycles of PCV [32]. Samples from 86 % of patients were available for analysis for 1p/19q codeletion. At the time of first report, the PFS was better in the PCV group, but OS was similar. Patients with 1p/19q deletion had better outcomes, irrespective of therapy. In addition, MGMT promoter methylation was of prognostic value in this cohort [33, 34]. Long-term follow up in patients with the 1p/19q codeletion showed that the addition of PCV to RT significantly increased PFS (median 157 vs. 50 months) and there was a trend toward increase in OS (OS not reached in the RT/PCV group vs. 112 months in the RT group HR 0.56; 95 % CI 0.31–1.03) [35].

Temozolomide has produced high response rates in patients with anaplastic oligodendroglioma. In 27 newly diagnosed patients treated with TMZ prior to radiotherapy the objective response rate was 33 % and the 6-month progression rate was 10 % [36]. An international intergroup trial is being conducted in patients with newly diagnosed grade III glioma with 1p/19q status codeletion (NCT00887146). Patients are randomized to three arms, TMZ alone (phase II group); or radiotherapy with concomitant and adjuvant TMZ or radiotherapy with adjuvant procarbazine, lomustine and vincristine (PCV) (phase III).

Chemotherapy for recurrent anaplastic oligodendroglioma

Both PCV and TMZ have activity in patients that recur after radiotherapy although generally response rates are lower and the duration of disease control is shorter. The activity of TMZ was seen in a study of 48 patients with anaplastic oligodendroglioma/oligoastrocytoma who progressed on PCV [37]. The objective response rate was 44 %, including 17 % who achieved complete remission. The median PFS was 7 months and the median OS was 10 months. Although there is no direct comparison of TMZ and PCV to determine which regimen is superior in terms of efficacy, the absence of cumulative myelosuppression with TMZ makes it the preferred choice in the setting of recurrent disease.

Anaplastic astrocytoma (WHO grade III)

The role of chemotherapy in anaplastic astrocytoma is not well established. Most phase III trials have demonstrated no benefit of chemotherapy compared with radiation alone in this tumor type. Carmustine and PCV are associated with minimal improvement in survival [38]. The Glioma Meta-Analysis Trialists' group showed a 6 % increase in 1- and 2-year survival for patients who received chemotherapy (2-year survival of 37 vs. 31 %) in a meta-analysis [39]. A large randomized trial of adjuvant PCV compared with RT alone did not show any benefit of adjuvant PCV [40]. The RTOG-9813 was a phase III study comparing radiation with BCNU or CCNU to radiation with TMZ, and the results of this study are pending.

The NOA-04 phase III trial compared the efficacy of RT followed by chemotherapy at progression, to initial chemotherapy followed by RT at progression, in newly diagnosed anaplastic gliomas [41]. Patients received conventional RT, PCV or TMZ as initial therapy. At disease progression or occurrence of unacceptable toxicity, patients in the RT arm received PCV or TMZ, whereas patients in chemotherapy arms were treated with RT. Median time to failure, PFS and OS were similar in all the treatment arms. Methylguanine DNA-methyltransferase (MGMT) promoter methylation and *IDH1* mutations were included in the correlative part of the study due to their prognostic value [42–44]. Patients with hypermethylation of the MGMT promoter had prolonged PFS both in the RT and the chemotherapy arm. Hypermethylation of MGMT promoter, *IDH1* mutations and oligodendroglioma histology was associated with a decreased risk of progression. The study demonstrated the prognostic value of IDH1 mutations in anaplastic gliomas, with a favorable impact that was more significant than that of 1p/19q codeletion or MGMT promoter methylation [41].

A large international trial, CATNON is being conducted in patients with newly diagnosed grade III glioma stratified by 1p/19q status. Nondeleted patients are randomized to radiation

with or without TMZ; following radiotherapy there is a second randomization to adjuvant TMZ or not.

Chemotherapy for recurrent anaplastic astrocytomas

Studies of both nitrosourea-based approaches and TMZ have demonstrated efficacy in recurrent anaplastic astrocytomas. A study of TMZ in recurrent anaplastic astrocytoma demonstrated a response rate of 35 % for patients who were chemotherapy naive and 20 % for patients who had received nitrosourea-based therapy [45]. This led to accelerated approval for TMZ by the US Food and Drug Administration. Based on activity of bevacizumab in recurrent glioblastoma, it is often used in patients with recurrent anaplastic astrocytoma [46]. A retrospective study reported a 64 % radiographic response and 6-month PFS rate of 60 % in 25 patients [47].

Glioblastoma (WHO grade IV)

Over the last decade there were a considerable number of investigational studies performed and reported in patients with glioblastoma. In a landmark study of approximately 600 patients, patients were randomized to RT alone (60 Gy in daily 30 fractions) or in combination with concurrent TMZ (75 mg/m^2 daily up to 49 days) and followed by up to six cycles of adjuvant TMZ (150–200 mg/m^2 daily for 5 days, every 28 days). There was statistically significant increase in OS in the combination arm compared with RT alone [27 vs. 11 % at 1 year, hazard ratio (HR) for death 0.63] [48]. Median and 2-year survival was increased by 2.5 months and 16.1 %, respectively [48]. This study provided level 1 evidence favoring use of TMZ for patients with newly diagnosed glioblastoma (Table 1). Accompanying correlative study demonstrated that methylation of the promoter region of the *MGMT* gene in the tumor was associated with superior survival, regardless of treatment received, but the benefit was primarily seen in methylated patients [42]. The 2-year survival rates were 49 and 24 % with combination therapy and with RT alone, respectively, in patients with MGMT methylation. The 2-year survival rates were 15 and 2 %, respectively in those without MGMT methylation. Preclinical work suggested that different prolonged schedule of TMZ may overcome chemotherapy resistance that led to studies looking at alternative dosing of TMZ in the newly diagnosed setting and at the time of recurrence [49, 50]. A large phase III randomized international study led by the RTOG compared the standard treatment versus a 21- or 28-day adjuvant TMZ schedule [51]. Dose-dense TMZ failed to result in improved efficacy regardless of tumor methylation status but was associated with more profound lymphopenia and fatigue. Strategies to increase the therapeutic ratio of existing chemotherapies, such as the inhibition of DNA repair enzymes [i.e., poly[ADP-ribose] polymerase (PARP) or base excision repair] are being evaluated. These agents are being combined with radiation and chemotherapy to increase the cytotoxicity of the combination approach [52–54].

The evaluation of chemotherapy in the elderly glioblastoma patient has been the focus of several recent trials. More than half of all patients with GBM are aged 65 years or older at the time of diagnosis, and the incidence rate of GBM in patients aged over 65 years is increasing rapidly. In addition, age is a well-known prognostic factor in this disease and the median survival for elderly GBM patients is <6 months. The use of chemotherapy for

elderly GBM patients remains controversial and several factors should be considered including age, MGMT methylation status, performance score, medical co-morbidities and patient preferences. Concurrent and adjuvant TMZ along with RT to 60 Gy have not been prospectively studied among patients aged over 70 years but should be considered for patients aged 65–70 years with excellent KPS [48]. Several approaches to shorten the duration of radiation (hypofractionated radiation) or to use chemotherapy alone have been evaluated. Based on recent randomized trials, testing for O6-methylguanine-DNA-methyltransferase (MGMT) promoter methylation should be performed routinely immediately after surgery to aid in adjuvant treatment decisions [55, 56]. For patients aged over 70 years with favorable KPS, or patients aged 60–70 years with borderline KPS, monotherapy utilizing standard TMZ dosing for patients with MGMT-methylated tumors, and hypofractionated RT (34 Gy in ten fractions or 40 Gy in 15 fractions) for patients with MGMT-unmethylated tumors should be considered. For elderly patients with poor KPS, reasonable options include best supportive care, TMZ alone or hypofractionated RT alone [55–57]. The role of concurrent TMZ with hypofractionated RT is being evaluated in an ongoing European Organization for Research and Treatment of Cancer/National Cancer Institute of Canada trial.

Targeted therapies for glioblastoma including anti-angiogenic approaches

The last decade has witnessed considerable progress being made in the understanding of the genetic and molecular pathogenesis of gliomas. This has in turn led to the identification of new potential therapeutic targets and the development of signaling pathway modulators.

Glioblastoma is a highly vascular tumor that is dependent on microvascular proliferation for survival and research into angiogenesis and its blockade have been among the top priorities in the last decade. The most important mediator of angiogenesis in glioblastoma is vascular endothelial growth factor (VEGF). Two trials, the BRAIN study and the NCI study showed that treatment with the anti-VEGF monoclonal antibody bevacizumab resulted in dramatic radiological responses and prolonged PFS relative to historical controls [58, 59]. Based on the response rates seen in the BRAIN study, which was a randomized noncomparative phase II study of 167 patients who were treated with bevacizumab alone or with irinotecan, and the NCI led single arm phase II study of bevacizumab alone, the US Food and Drug Administration granted accelerated approval to bevacizumab for recurrent glioblastoma in 2009 [46]. The PFS at 6 months was 43 and 50 % for bevacizumab alone and the combination arm in the BRAIN study respectively. The objective response rates were 28 and 38 % for the two arms and the OS was 9.2 and 8.7 months, respectively. The NCI study demonstrated a PFS at 6 months of 29 % and a radiographic response rate of 35 % with bevacizumab. The most common side effects associated with bevacizumab include fatigue, headache, and hypertension. A number of studies have examined whether additional chemotherapy or targeted therapy to bevacizumab translates into additional efficacy compared to bevacizumab alone. A Phase II trial (CABARET) evaluated the efficacy of adding carboplatin to bevacizumab in recurrent glioblastoma. The PFS at 6 months was 26 % and OS was 6.9 months for the combination versus 6-month PFS of 24 % and OS of 6.4 months for bevacizumab alone [60]. The addition of chemotherapy or targeted therapy has failed to show any added benefit in recurrent GBM trials with the exception of the BELOB

study. In the BELOB study, a three-arm multicenter randomized phase II study, 148 recurrent glioblastoma patients received bevacizumab alone, lomustine alone or the combination of the two. OS at 9 months was 38, 43 and 59 % and the PFS-6 was 16, 13 and 41 % in the three arms respectively [61]. EORTC 26101 will assess the role of bevacizumab and lomustine versus lomustine alone in a randomized phase III trial in recurrent GBM.

The benefit of bevacizumab in recurrent glioblastoma prompted its evaluation in the treatment of newly diagnosed glioblastoma. There are several small single-arm phase II studies of the combination of bevacizumab with radiation and TMZ in the newly diagnosed setting [62]. Two large randomized trials evaluated the benefit of addition of bevacizumab to RT and TMZ. The first study, RTOG 0825 was a randomized, double-blinded, placebo controlled trial and was conducted primarily in the United States. In this study the addition of bevacizumab resulted in longer PFS that did not reach the preset level of significance (10.7 vs. 7.3 months, HR 0.79). There was no difference in OS between two arms (16.1 vs. 15.7 months, HR 1.13) [63]. The AVAglio study was an industry-sponsored, international, multicenter Phase III placebo-controlled randomized trial in newly diagnosed glioblastoma [64]. This study demonstrated that the addition of bevacizumab to RT and TMZ produced a clinically meaningful and statistically significant improvement in PFS (HR 0.64, $p < 0.0001$; median 10.6 vs. 6.2 months) as compared to RT and TMZ. However similar to the RTOG 0825 there was no difference in median survival (16.7 months for the placebo group; 16.8 months for the bevacizumab group. HR 0.88, $p = 0.0987$).

The open-label GLARIUS trial was a randomized, multicenter study of MGMT-nonmethylated GBM. The patients were randomized in a 2:1 manner to receive bevacizumab during RT that was followed by maintenance bevacizumab and irinotecan compared to standard therapy of 6 weeks of concurrent RT and TMZ followed by 6 cycles of adjuvant TMZ [65]. Preliminary results of this study demonstrated a PFS-6 rate of 71.1 % in the experimental arm compared to 26.2 % in the control arm ($p < 0.0001$ log rank test). Final results are pending.

Despite improvement in PFS, there has been no benefit in OS with bevacizumab possibly due to resistance that can be due to intrinsic or acquired (evasive) mechanisms. Hence a number of strategies have tested combination of bevacizumab with other targeted agents, or evaluating agents that target other antiangiogenic pathways such as platelet-derived growth factor (PDGF), integrins or hepatocyte growth factor (HGF). Despite promising results in a phase II study of cediranib (AZD2171), an orally administered pan-VEGF receptor inhibitor [66], a Phase III randomized trial (REGAL) that compared the efficacy of cediranib either as monotherapy or in combination with lomustine failed to show any improvement in PFS compared to lomustine alone in recurrent GBM [67] (Table 2). VEGF Trap (aflibercept) in a phase II study showed minimal evidence of single-agent activity in unselected patients with recurrent malignant glioma [68].

Cilengitide is a cyclic pentapeptide that selectively competitively inhibits the aVb3 and aVb5 integrins and has antiangiogenic properties [69, 70]. Cilengitide showed initial promise in recurrent GBM studies that led to its evaluation in two large newly diagnosed studies [69, 70]. The CORE study evaluated the efficacy of cilgentide in the unmethylated

MGMT gene promoter in a multicenter, randomized phase II trial. The study showed a median OS of 16.3 months in the cilengitide arm compared to a median OS of 13.4 months in the control-group (HR 0.69; $p = 0.033$). The CENTRIC study was a phase III trial that looked at the benefit of cilengitide combined with RT and TMZ for newly diagnosed glioblastoma with *MGMT* promoter methylation [71]. The study failed to show any additional benefit of cilengitide in this patient population [71]. Median OS was 26.3 months in both arms and median PFS was 13.5 months in the cilengitide arm and 10.7 months in the control arm ($p = 0.87$). This drug is not being further developed.

The other antiangiogenic agents that have undergone investigation in recurrent glioblastoma include multi-targeted tyrosine kinase inhibitors such as sunitinib, sorafenib, cabozantinib and enzastaurin, an inhibitor of protein kinase C-beta that targets VEGF, as well as the mTOR pathway [72]. The outcomes of the studies with these agents have been similar or inferior compared to those seen with bevacizumab [72–74].

The EGFR pathway can be dysregulated in up to 40 % of glioblastoma and number of phase I and II trials of erlotinib and gefitinib for recurrent high-grade gliomas evaluated the efficacy of these agents. However, the results of most of these trials were disappointing and showed limited activity for these agents [75–78]. There were reports that tumors with the variant 3 mutant (EGFRvIII), with resulting constitutive activation of EGFR tyrosine kinase activity, along with intact phosphatase and tensin analogue (PTEN) may be more responsive to EGFR inhibitors [79]. Two studies adding erlotinib to RT and TMZ for newly diagnosed glioblastoma did not show an improvement in survival [80, 81]. The cooperative group study, RTOG 0211 evaluated the benefit of RT with concurrent gefitinib and did not show an improvement in survival [82]. Irreversible EGFR inhibitor, afatinib did not show clinical benefit either alone or in combination with TMZ in patients with recurrent GBM [83]. There is an ongoing phase II study with dacomitinib, a second-generation EGFR inhibitor, in patients with recurrent glioblastoma.

Clinical trials of other targeted agents including the mTOR inhibitors everolimus and temsirolimus, and the farnesyl transferase inhibitor, tipifarnib, have shown limited efficacy in recurrent high-grade gliomas [84–88]. Studies using epigenetic modulation through histone deacetylase inhibitors and the proteasome inhibitor bortezomib have revealed minimal efficacy of these approaches [89, 90].

The future of medical treatment of gliomas

Precision medicine

As treatment for gliomas evolve in the ensuing years, studying the biological behavior of these tumors in the context of therapeutic options is increasingly important. Precision therapy that is tailor-made treatment around the molecular evolution of these tumors will require employment of high-throughput genomic technology in the clinical setting. The brain tumor centers of excellence will need to institute effective workflow that encompass tissue collection after surgery, proper as well as prompt processing, and standardization of biomaterial extraction. The tissue will require sequencing (combination of targeted capture sequencing, whole genome sequencing, and RNA sequencing), and data analysis that will

lead to therapeutic recommendations for each individual will be a critical component to translate the information to the clinical management of the patient. The genomic profiling can not only inform diagnosis and but alter treatment approach as more targeted agents are available in the future.

Molecular characterization of the gliomas

The recent molecular characterization of gliomas has clarified a framework of different subtypes of these tumors and has revealed pathways that will help the development of more effective targeted therapies. The diagnosis of gliomas in the past was based on a complete clinicopathological assessment. Although this is a valuable approach that permits the distinction of different grades within categories of the same tumor type, such as astrocytomas, that may predict clinical outcome, it does not address the issue that distinct genetic subgroups may exist within each grade.

In recent years there has been extensive work in large-scale gene expression profile studies in glioblastoma to characterize the molecular subtypes of GBM that include a report of the Cancer Genome Atlas Research Network [91]. These genomic analyses provided insights underlying tumor biology that further classify different subtypes that may inform treatment plans, impact patient outcome, and improve response to treatment [92, 93]. Verhaak et al. [93] classified glioblastoma into proneural, neural, classical, and mesenchymal subtypes based on gene expression profiles of these tumors. Aberrations and differential gene expression of *EGFR*, *NF1*, and *PDGFRA*/*IDH1* help define the various subtypes and these pathways can be targeted using novel therapies. The work in genome and transcriptome shows that glioblastoma is a heterogeneous tumor with multiple redundant pathways and distinct subtypes [94].

Considerable research in genetic alterations in WHO grade II astrocytoma in adults has shown the role of inactivation of the TP53 tumor suppressor gene, heterozygous point mutations of the IDH1, and loss of chromosome 22q in these tumors. TP53 on chromosome 17p encodes the p53 protein that has an important role in a numerous cellular processes, including apoptosis, cell cycle arrest, and response to DNA damage [95]. Somatic mutations in IDH1 are present in 50–80 % of WHO grade II and III astrocytic tumors and oligodendroglial tumors in adults and up to 5 % of the secondary glioblastomas [44, 96]. These mutations lead to conversion of α-ketoglutarate into D-2-hydroxyglutarate, an oncometabolite that drives the oncogenic activity of IDH mutations [97]. Patient with tumors with IDH mutations have better outcomes than do IDH-wild-type gliomas of the same histological grade [98, 99]. Recent discoveries of pathogenic mutations in *IDH1* [97], *IDH2*, *ATRX* [100], *CIC* [101], and *FUBP1* [101], have helped genomic characterization of low grade gliomas. These mutations form the framework of molecular pathogenesis of these tumors and offers robust markers that not only enhance classification but also guide treatment. Common cytogenetic alteration in oligodendroglial histology consists of an unbalanced t(1;19)(q10;p10) translocation that results in combined loss of chromosomal arms 1p/19q and leads to the loss of one hybrid chromosome and thus loss of heterozygosity [22]. Tumors with 1p/19q-codeletions have a better prognosis than do histologically identical tumors of the same grade that do not harbor this codeletion [102]. The key to

successful treatment of these tumors will lie in the realization that these molecularly defined subsets are different disease entities and it is likely that specific targeted therapies aimed at the driver mutations will be more likely to be efficacious. In the future, the molecular classification of these tumors will be performed routinely and be defined in clinically relevant terms based on the identification of markers that define subsets and guide therapeutic options.

The next 10 years

The advances in imaging, improved targeted therapeutic options, and routine availability of molecular characterization of tumors will enhance glioma management in the next decade. A great deal of progress has been made in the last decade in the understanding of the molecular mechanisms of gliomas. The continuation of these efforts may further classify the subtypes of tumors of the same grade and warrant different therapeutic options for the patients. Accelerated developments of new drugs will likely aid improvements in therapeutic outcomes in the next 10 years. Given the complex network of pathways involved, one approach would be the use of multitargeted therapy that simultaneously aims at different constitutive pathways driving the malignancy. Further developments in drug delivery will play a key role in translating this into improved patient outcomes. While the next decade appears to be promising, considerable work involving the multidisciplinary collaboration of basic science, translational and clinical investigators will need to be done to improve the outcome of patients with gliomas.

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Table 1

Newly diagnosed glioblastoma phase III trials—level 1 evidence

Study (reference)	Number of patients/treatment arm	Treatment arms	PFS	OS	Comments
EORTC/NCI [48]	287 versus 286	RT/TMZ + TMZ versus RT	6.9 versus 5.0 months	14.6 versus 12.1 months	RT/TMZ + TMZ is superior to RT alone
RTOG 0525 [51]	411 versus 422	Standard dose TMZ (days 1–5 every 28 days) versus dose dense TMZ (days 1–21 every 28 days)	5.5 versus 6.7 months	16.6 versus 14.9 months	Dose dense and standard 5 day TMZ are equivalent in efficacy regardless of methylation status
RTOG 0825 [63]	320 versus 317	RT/TMZ/Bev + TMZ/Bev versus RT/TMZ + TMZ	10.7 versus 7.3 months	15.7 versus 16.1 months	PFS was longer in Bev group; however there was no significant difference in OS
AVAglio [64]	458 versus 463	RT/TMZ/Bev + TMZ/Bev versus RT/TMZ + TMZ	10.6 versus 6.2 months	16.9 versus 16.8 months	PFS was longer in Bev group; however there was no significant difference in OS
CENTRIC [71]	272 versus 273	RT/TMZ/CIL + TMZ/CIL versus RT/TMZ + TMZ	13.5 versus 10.7 months	26.3 versus 26.3 months	CIL did not prolong PFS or OS in methylated MGMT gene promoter GBM

PFS progression free survival, *OS* overall survival, *RT* radiation therapy, *TMZ* temozolomide, *Bev* bevacizumab, *CIL* cilengitide

Table 2

Recurrent glioblastoma phase III trials—level 1 evidence

Study (reference)	Number of patients per treatment arm	Treatment	PFS	OS	Comments
Enzastaurin versus lomustine in glioblastoma [72]	174 versus 92	Enzastaurin versus lomustine	1.5 versus 1.6 months	6.6 versus 7.1 months	Enzastaurin did not have superior efficacy compared with lomustine in recurrent GBM
REGAL [67]	131 versus 65 versus 129	Cediranib versus lomustine versus cediranib/lomustine	92 versus 82 versus 125 days	8.0 versus 9.8 versus 9.4 months	Cediranib alone or cediranib in combination with lomustine does not have superior efficacy compared with lomustine in recurrent GBM

PFS progression free survival, *OS* overall survival