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Radiosensitizers in the temozolomide era for newly diagnosed glioblastoma

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Abstract

Glioblastoma (GBM) is a challenging diagnosis with almost universally poor prognosis. Though the survival advantage of postoperative radiation (RT) is well established, around 90% of patients will fail in the RT field. The high likelihood of local failure suggests the efficacy of RT needs to be improved to improve clinical outcomes. Radiosensitizers are an established method of enhancing RT cell killing through the addition of a pharmaceutical agent. Though the majority of trials using radiosensitizers have historically been unsuccessful, there continues to be interest with a variety of approaches having been employed. Epidermal growth factor receptor inhibitors, histone deacetylase inhibitors, antiangiogenic agents, and a number of other molecularly targeted agents have all been investigated as potential methods of radiosensitization in the temozolomide era. Outcomes have varied both in terms of toxicity and survival, but some agents such as valproic acid and bortezomib have demonstrated promising results. However, reporting of results in phase 2 trials in newly diagnosed GBM have been inconsistent, with no standard in reporting progression-free survival and toxicity. There is a pressing need for investigation of new agents; however, nearly all phase 3 trials of GBM patients of the past 25 years have demonstrated no improvement in outcomes. One proposed explanation for this is the selection of agents lacking sufficient preclinical data and/or based on poorly designed phase 2 trials. Radiosensitization may represent a viable strategy for improving GBM outcomes in newly diagnosed patients, and further investigation using agents with promising phase 2 data is warranted.

Keywords

glioblastoma | glioma | newly diagnosed | radiosensitizer | temozolomide

Glioblastoma (GBM) is the most common primary malignant brain tumor in adults, comprising 45.6% of new malignant brain tumors, with an incidence rate of 3.19 per 100 000 individuals.[1] Current standard of care for GBM is combined modality therapy involving maximal safe resection and postoperative radiation (RT) given concurrently with temozolomide (TMZ) followed by an additional 6 to 12 months of adjuvant TMZ.[2] The rationale behind combined modality therapy involves overcoming challenges unique to GBM's intracranial location, namely limitations of resection due to morbidity and mortality, acute and late treatment-related toxicity, and limited blood-brain barrier penetration and the corresponding resistance to systemic therapy.[3] Although current combined modalities demonstrated a survival advantage over RT alone, outcomes remain poor and relapse is considered inevitable.[4]

Maximal safe resection is first-line therapy for GBM, and surgical resection is presumed to have the largest impact on patient survival, but a complete resection is rare because of the infiltrative nature of the disease. Comparison of radiographic and neuropathology findings have shown that isolated tumor cells can be present, unassociated with the edema see on imaging, far outside the gross tumor volume.[5] Adjuvant RT is

used to treat this microscopic disease. Analysis of previous Brain Tumour Study Group and Medical Research Council studies confirmed 60 Gy as the minimum effective dose in GBM.[6,7] Though the survival benefit of postoperative RT is well established,[8] in patients treated with RT alone around 90% of patients will fail in the RT field.[9,10]

This high probability of local failure suggests the need, and opportunity, to improve the efficacy of RT to improve clinical outcomes. Strategies to improve local control including altered fractionation schemes[11]; dose escalation with boost,[12] stereotactic radiotherapy,[13] biodegradable carmustine wafers,[14] and brachytherapy[15] have failed to demonstrate a survival benefit. Many of these techniques lead to an increased incidence of necrosis and higher rates of reoperation, which can potentially increase patient toxicity and decrease survival.

The addition of pharmaceutical agents presents an alternative method to increase the effectiveness of RT by enhancing RT cell killing. Unfortunately, though the rationale behind this approach is sound, historically nearly all trials of radiosensitizers in upfront GBM treatment have been unsuccessful (Table 1). However, in the TMZ era, there continues to be interest in the use of radiosensitization to treat upfront GBM. Strategies have varied, with a particular focus on epidermal growth factor receptor (*EGFR*) inhibitors, histone deacetylase (HDAC) inhibitors, antiangiogenic agents, as well as other molecularly targeted agents as potential methods of increasing the efficacy of RT. Here we review the phase 2 studies that have reported the addition of a radiosensitizer in combination with standard RT plus TMZ, focused on several reported outcomes including toxicity (both acute and late), efficacy, and the ability of the patient to complete the standard portion of his or her therapy.

Epidermal Growth Factor Receptor Inhibition

EGFR is an important mitogen for newly diagnosed GBM, and amplification of this gene is found in approximately 40% of cases.[30] The overexpression of *EGFR* in GBM correlates with decreased apoptosis, increased cellular proliferation, tumorigenesis, and poor prognosis. It has also been shown to correlate with resistance both to biodegradable carmustine chemotherapy and radiotherapy.[31,32] As such, *EGFR* is a potential target for inhibition to increase sensitivity to RT.

Erlotinib is an oral tyrosine kinase inhibitor of the human EGF receptor that is FDA approved for the treatment of non–small cell lung and pancreatic cancers. It is considered an appealing molecular agent because of its targeting of both the wild-type and the most common mutant form of *EGFR* in GBM, the *EGFRvIII* mutant.[33] Three phase 2 studies have examined the role of erlotinib given concurrently with RT plus TMZ and have demonstrated widely discordant results. This was true both for survival and toxicity outcomes. The first reported study of 97 patients had 2 patients with grade 5 toxicities either near the end or shortly after RT, 24 grade 4, and 105 grade 3 toxic events. The addition of erlotinib demonstrated no significant survival benefit compared to RT plus TMZ–era controls, with a median survival of 15.3 months.[17] In this study, 84% of the patients were able to complete the study drug but there was no comment on any potential delay of the RT and TMZ. The second trial reported less toxicity, with no grade 5 and 5 grade 4 toxicities in a cohort of 65 patients. This study reported that patients treated with erlotinib and RT plus TMZ had a median survival of 19.3 months and a 6-month progression-free survival (PFS) of 73%, concluding there was an improvement compared to historical controls.[18] There was no reporting of RT delays due to the combination therapy. The last study reported that patients who received erlotinib had worse survival outcomes, with a median survival of only 8.6 months and a 6-month PFS of 30%. This study was closed prematurely because of excessive toxicity, with a total of 4 patient deaths and 3 deaths deemed directly related to treatment.[19] It is unclear what is responsible for these contrasting results. Though there were differences in the regimens used to administer erlotinib, the daily dosages were similar, with the highest allowable dose in the study showing the least amount of toxicity. Of note, late toxicity of this novel combination was not reported in any of the 3 trials.

An alternative strategy for the targeting of the *EGFR*/phosphatidylinositol-3 kinase (PI3K) pathway is inhibition of mammalian target of rapamycin (mTOR), which is a downstream regulator of this pathway with 2 separate complexes (mTORC1 and mTORC2). When activated, mTOR can regulate cell size and growth as well as Akt activation.[34] Activating mutations of the Akt-mTOR pathway have been associated with TMZ treatment and are thought to confer resistance to this therapy through the binding and stabilizing of MGMT (O^6-methylguanine-methyltransferase).[35,36] Everolimus is an oral inhibitor of mTOR, and animal studies have shown that mTOR inhibition radiosensitizes several tumor cell lines including GBM.[37,38]

Two separate, multi-institutional phase 2 studies have investigated the use of everolimus in combination with standard RT plus TMZ, with distinctive designs but similar outcomes in terms of survival (although not toxicity). The North Central Cancer Treatment Group (NCCTG) N057K trial was a single-arm study in which weekly everolimus was given concurrently with RT plus TMZ and continued adjuvantly with the TMZ until disease progression. The addition of weekly everolimus was moderately toxic, with a single death on treatment due to febrile neutropenia. Twenty-five patients had at least 1 grade 3 to 4 nonhematologic toxicity, and 24 and 21 patients had grade 3 or 4 nonhematologic toxicity, respectively. Median PFS and overall survival (OS) were 6.4 months and 15.8 months, respectively. Late toxicity was not reported, nor was 6-month PFS. Though survival was similar to historical phase 2 trials, the NCCTG N057K trial's 12-month OS of 64% did not meet the predetermined end point of 65%.[20]

The Radiation Therapy Oncology Group (RTOG) 0913 trial was a randomized study of daily everolimus with upfront chemoradiation (CRT) for GBM.[21] Though the NCCTG N057K authors had hypothesized that daily dosing may improve the efficacy of everolimus, this trial showed not only did it not have a survival benefit but it also carried statistically significantly increased toxicity. There were 108 grade 3, 39 grade 4, and 10 grade 5 toxicities in the everolimus arm, which was a statistically significant increase over the control arm. Etiology of grade 5 toxicity

Table 1 Completed Trials of Radiosensitizers in the Temozolomide Era

First Author	NCT No.	Design	Patients, No.	Drug	Completed Study Drug + RT plus TMZ, %	Grade 3 Toxicity, n	Grade 4 Toxicity, n	Grade 5 Toxicity, n	Late-Grade 3 to 5 Toxicity, %	Delayed RT, %	6-Mo PFS, %	Median PFS, mo	Median OS, mo
Stupp, 2002[16]		Phase 2 single-arm	64	TMZ	86	22	40	–	–	30	–	–	16
Stupp, 2005[4]	NCT00006353	Phase 3 randomized	287	TMZ	85	7% grade 3/4	–	–	1	32	54	–	14.6
Brown, 2008[17]	NCT00039494	Phase 2 single-arm	97	Erlotinib	84	105	24	2	–	–	–	7.2	15.3
Prados, 2009[18]	NCT00187486	Phase 2 single-arm	65	Erlotinib	–	43	5	0	–	–	73	8.2	19.3
Peereboom, 2010[19]	NCT00274833	Phase 2 single-arm	28	Erlotinib	74	31	5	4	–	–	30	2.8	8.6
NCCTG N057K Ma, 2015[20]	NCT00553150	Phase 1/2 single-arm	100	Everolimus	78	–	–	1	–	–	–	6.4	15.8
RTOG 0913 Chinnaiyan, 2018[21]	NCT01062399	Phase 1/2 randomized	171	Everolimus	–	108	39	10	–	–	–	8.2	16.5
Krauze, 2015[22]	NCT00302159	Phase 2 single-arm	37	Valproate	67	16	6	0	2[23]	0	70	10.5	29.6
Galanis, 2018[24]	NCT00731731	Phase 1/2 single-arm	107	Vorinostat	–	106	47	3	–	–	–	8.0	16.1
Butowski, 2011[25]	NCT00402116	Phase 1/2 single-arm	66	Enzastaurin	–	66% grade 3/4	–	5	–	–	65	8.4	17.3
Lee, 2015[26]	NCT00441142	Phase 1/2 randomized	76	Vandenatib	67	93 ≥ grade 3	–	1	–	–	58	7.7	16.6
Butowski, 2005[27]		Phase 2 single-arm	61	13-cis-retinoic acid	92	18	8	0	–	–	38	4.9	13.3
Grossman, 2009[28]		Phase 2 single-arm	72	Talampanel	–	38	15	1	–	–	–	–	18.3
Kong, 2018[29]	NCT00998010	Phase 2 single-arm	24	Bortezomib	–	9	1	0	–	–	54	6.2	19.1

Abbreviations: NCCTG, North Central Cancer Treatment Group; NCT, national clinical trial; OS, overall survival; PFS, progression-free survival; RT, radiation; RTOG, Radiation Therapy Oncology Group; TMZ, temozolomide.

Table 2 Ongoing Trials of Radiosensitizers

	Intervention			Study Population	No.	Estimated Start Date	Estimated Completion	Location
1	Lapatinib	NCT01591577	Dual tyrosine kinase inhibitor that interrupts the HER2/*neu* and epidermal growth factor receptor pathways	Newly diagnosed glioblastoma multiforme or gliosarcoma	70	December 7, 2012	December 7, 2019	Jonsson Comprehensive Cancer Center
2	ABI-009	NCT03463265	Nanoparticle albumin-bound rapamycin	Recurrent high-grade glioma and newly diagnosed glioblastoma	56	August 1, 2018	June 2021	John Wayne Cancer Institute

Abbreviations: ABI-009, nab-rapamycin; NCT, national clinical trial.

included lung infection, meningitis, scrotal infection, other neoplasms, respiratory failure, intracranial hemorrhage, and a death not otherwise specified. In addition to unacceptable toxicity, survival outcomes were worse with everolimus compared with the control arm. Median OS for the experimental arm was 16.5 months, which was comparable to historical controls but inferior to the experiment's control arm. The 6-month PFS was not reported, but median PFS was 8.2 months in the everolimus arm compared with 10.2 months without. The investigators were unable to explain the superior survival of the control arm compared with historical standards because the treatment arms were well matched. Investigation is ongoing to determine factors that may have contributed to this disparity.

The authors of both trials explained the apparent lack of benefit of everolimus in upfront GBM treatment as incomplete target inhibition. Though everolimus is a selective inhibitor of mTORC1 alone, model systems have shown that this inhibition can result in increased AKT activation through the activation of mTORC2.[39] Therefore, strategies that target both mTORC1 and mTORC2 are needed.[40] However, given the pronounced toxicity seen with everolimus it is unlikely that this drug will be a component of such strategies.

Histone Deacetylase Inhibitors

HDACs are a family of enzymes responsible for the removal of acetyl groups from histones and other cytoplasmic and nuclear proteins. Studies with HDAC inhibitors such as valproic acid (VPA) have shown selective increases in tumor cell RT sensitivity using both in vitro and in vivo model systems. Though the specific mechanism of radiosensitization is unclear, it is speculated that it is from inhibition of double-strand break repair, specifically chromatin remodeling late in the process.[41,42] VPA is a nonhepatic, enzyme-inducing antiepileptic drug, with reported safe long-term usage and several retrospective clinical series showing prolonged survival with its addition to RT and TMZ.[43–45]

Krauze et al[22] conducted a phase 2 trial adding 25 mg of VPA per kilogram divided into 2 daily doses concurrent with RT plus TMZ. VPA therapy was initiated 1 week prior to treatment at 10 to 15 mg/kg/d and subsequently increased to 25 mg/kg/d and continued until the completion of RT. Of 37 patients, 81% completed treatment with VPA, whereas 67% completed treatment as prescribed. According to the CTCAE (Common Terminology Criteria for Adverse Events) version 3 and the Radiation Morbidity Scoring Scheme, 6 patients experienced grade 4 acute toxicity, all blood or bone marrow, and there were no deaths on treatment. There were only 2 grade 3 to 5 late toxicities; 1 blood or bone marrow and 1 pain, both grade 3 in severity, and neither probably or possibly attributed to concurrent VPA plus RT plus TMZ.[23] Median OS was 29.6 months and 6-month PFS was 70%. The authors concluded that VPA was well tolerated and may have benefit over historical controls.

Despite these promising outcomes, the role of VPA in newly diagnosed GBM remains controversial. A large pooled analysis of the AVAGlio (Avastin and Glioblastoma), CENTRIC (Cilengitide, Temozolomide and Radiation Therapy in treating Radiation Therapy and Methylated Gene Promoter Status), CORE (Cilengitide, Temozolomide and Radiation Therapy in treating Radiation Therapy and Unmethylated Gene Promoter Status), and Radiation Therapy Oncology Group 0825 trials found the use of VPA at antiepilepsy dosages was not associated with improved PFS or OS.[46] Although the phase 2 results had a set protocol for dosing and administration, the pooled analysis results included no information of VPA dose, and recorded only VPA and no VPA use at baseline or VPA use both at the start of and still after chemoradiotherapy.[47] As such, it is unlikely that the pooled analysis patients received VPA escalated to 25 mg/kg rather than lower doses more typical of antiseizure prophylaxis (5 to 10 mg/kg). Given the promising median survival and minimal toxicity found in the phase 2 trial, further investigation of VPA as a radiation sensitizer is warranted.

In addition to VPA, Vorinostat (suberoylanilide hydroxamic acid) is also an HDAC inhibitor and acts as a small-molecule inhibitor of most human class 1 and class 2 HDACs. Preclinical studies have shown that Vorinostat has antitumor activity against malignant glioma cells in combination with RT or other anticancer drugs.[48,49] One phase 1/2 trial has been performed exploring the effect of adding Vorinostat to standard adjuvant CRT but failed to meet its primary efficacy end point of improvement in OS at 15 months from 50% to 63%. The median OS was 16.1 months and median PFS was 8.0 months, although 6-month PFS was not reported. There were 47 incidents

of grade 4 toxicity and there were 3 deaths on treatment, all of which were deemed unlikely to be related to treatment. Late toxicity was not addressed. Although the study failed to meet its efficacy end point, the authors did comment that RNA sequencing data suggested that gene signatures may be able to identify patients who may benefit from the addition of Vorinostat to standard RT plus TMZ. Specifically, RNA sequencing data of baseline tumor samples suggested an association between previously identified Vorinostat signatures, and PFS and OS.[22]

Antiangiogenic Therapy

Angiogenesis is a hallmark of GBM because its rapid proliferation requires new blood vessels to survive. The vascular endothelial growth factor (VEGF) pathway is the primary driver of this process.[50] Though attempts to inhibit VEGF with bevacizumab have not demonstrated any improvement in OS in phase 3 trials,[51,52] investigations of alternate ways of inhibiting the pathway are ongoing.

The protein kinase C (PKC) family of enzymes is essential to tumor growth and proliferation, and the beta isoform of PKC is a part of the VEGF pathway that is upregulated in GBM.[53,54] Enzastaurin is a selective serine/threonine kinase inhibitor of PKC that can block tumor growth and angiogenesis[55] and has demonstrated enhancement of RT- and TMZ-induced cell death in GBM cell lines.[56] A single study has investigated the use of enzastaurin in newly diagnosed GBM in a cohort of 66 patients who were studied and compared to a historical cohort of 193 patients enrolled in previous University of California, San Francisco studies.[24] Enzastaurin was given both concurrently with CRT as well as daily for 12 months adjuvantly or until unacceptable toxicity or disease progression. Median OS was 17.3 months for patients treated with enzastaurin, and 6-month PFS was 65%. No patients died during therapy, and although 5 deaths were reported within 30 days of therapy discontinuation, this was deemed due to progression of disease. Despite these deaths, OS was slightly improved for patients treated with enzastaurin compared to the historical controls of patients receiving RT plus TMZ alone. The authors concluded that when compared to similar phase 2 trials with survival approaching 20 months, there was no additional benefit of enzastaurin and that future studies appeared unrealistic.

In an effort to target complementary pathways, Vandetanib represents a combined approach, targeting both VEGF and EGFR. It is a low-molecular-weight receptor tyrosine kinase inhibitor of EGFR, VEGFR-3, VEGFR-2, and RET (rearranged during transfection) tyrosine kinases.[57-60] In preclinical models Vandetanib inhibited growth of glioma cells,[59,61] and combining Vandetanib with RT has demonstrated significant synergistic antitumor effect.[62]

A noncomparative, open-label, multicenter phase 2 study randomly assigned patients with newly diagnosed GBM to either standard CRT, or standard CRT with Vandetanib. The trial drug was initiated 5 to 7 days before beginning RT and was continued for 12 cycles of 28 days, or until study removal for unacceptable toxicity or disease progression. Late toxicity was not reported, and there were 93 grade 3 or greater acute toxicities. One patient in the Vandetanib arm suffered grade 5 pneumonia, with no deaths due to toxicity seen in the standard arm. PFS at 6 months was 58% in the trial arm and 57% in the control arm. The trial did not meet the primary end point of prolongation of OS (16.6 months) as compared with either the control arm (15.9 months) or historical controls and was terminated early because of futility based on an unplanned interim analysis.[25]

Additional Molecular Targets

Retinoic acid is active preclinically in glioma, inhibiting cell proliferation, inducing cellular apoptosis, although the mechanisms for these effects are unclear.[63] Preclinical studies have shown that retinoic acid enhances the radiosensitivity of glioma cells, although the precise mechanism is not understood.[64] A single phase 2 trial by the University of California, San Francisco group investigated the efficacy of combining retinoic acid with RT plus TMZ. Median OS was 57 weeks, and 6-month PFS was 38%. Overall, the treatment was well tolerated, with 8 incidents of grade 4 toxicity and 18 incidents of grade 3 toxicity. Late toxicity in this study was not reported. The authors concluded survival was comparable to those who received nitrosoureas (14.3 months)[26] but was worse when compared with standard CRT with TMZ alone.[26]

Glutamate is a major excitatory neurotransmitter in the mammalian CNS and is thought to play a role in the pathophysiology of events that lead to disturbed neuronal function and cell death in acute neurological diseases such as trauma, multiple sclerosis, stroke, and neurodegenerative disease.[65-67] Glioma cells not only have impaired uptake of glutamate, but also release large amounts of glutamate into the extracellular fluid.[68] AMPA (α-amino-2-hydroxy-5-methyl isoxazole-4-propionic acid) is one of several receptors of glutamate that is expressed in most high-grade gliomas and whose blockade has been shown to induce apoptosis and suppress migration of human GBM in vivo.[69] Talampanel is an allosteric antagonist of AMPA that has shown efficacy as an anticonvulsant in humans.[67] Owing to the role glutamate and AMPA may play in glioma pathology, a phase 2 trial using talampanel with concomitant CRT and adjuvant TMZ was undertaken. Median OS was 18.3 months in all patients, with methylated and unmethylated patients having survival of 29 and 16.9 months, respectively. There was 1 grade 5 acute toxicity due to febrile neutropenia, 15 grade 4 toxicities, and 38 grade 3 toxicities. There was no reporting on late toxicities or PFS.[27] The authors concluded that the inclusion of talampanel added no significant additional toxicity, and the survival results were encouraging. However, no further research on talampanel in newly diagnosed GBM has been reported. There has been one phase 2 trial investigating the activity of talampanel in recurrent GBM that showed that although it was tolerated it had no significant activity as a single agent in this setting.[70]

A recently reported phase 2 trial exploring molecular therapies as an adjunct to CRT shows promise. The ubiquitin-proteasome system is responsible for the degradation of 80% to 90% of intracellular proteins and is essential for maintaining cell homeostasis.[71] Disruption of this process permits unregulated cell growth and survival.[72,73]

Bortezomib (BTZ) is a proteasome inhibitor thought to work by suppression of the nuclear factor (NF)κβ signaling pathway. In times of stress, NFκβ binds to target genes and activates transcription of a variety of factors that induce cell growth and differentiation, and prevent apoptosis.[72] NFκβ inhibitor-α (NFκBIA) represses NFκβ, and deletion of the *NFκBIA* gene has been demonstrated to be a poor prognostic marker in GBM patients without *EGFR* amplification, suggesting that inhibition of this pathway may have a role in management of glial neoplasms.[74] Multiple studies on animal models have shown BTZ causes growth arrest in human GBM cell lines,[75–77] and a phase 1 trial demonstrated it was well tolerated when given alongside concurrent RT plus TMZ.[78]

Kong et al[28] recently published a small, single phase 2 study in which BTZ was given during both the concurrent and adjuvant phases of GBM treatment in newly diagnosed patients treated with RT plus TMZ. The addition of BTZ was well tolerated, with no grade 5 toxicity, a single grade 4 toxicity that was considered unrelated to treatment, and 9 grade 3 toxicities. Late toxicity was not reported. Though median PFS (6.2 months) and 6-month PFS (54.2%) were on a par with historical outcomes, longer-term outcomes were impressive, with a median OS of 19.1 months. The most pronounced survival advantage was in MGMT-methylated patients, with median OS of 61 months compared with 16.4 months in unmethylated patients. Though this was a small study of only 24 patients that did not reach the planned statistical power, the survival outcomes are compelling. The results of this trial suggest that further investigations of the addition of BTZ to RT plus TMZ in upfront GBM treatments are warranted.

Ongoing Trials

Several phase 2 trials are accruing to test new radiosensitizers in addition to RT plus TMZ. Jonsson Comprehensive Cancer Center is investigating the use of lapatinib, a dual tyrosine kinase inhibitor that interrupts the EGFR and Her2/*neu* pathways. ABI-009 (nab-rapamycin) is a macrolide antibiotic rapamycin-bound nanoparticle albumin that the John Wayne Cancer institute is testing both in progressive and newly diagnosed GBM in combinations with bevacizumab, lomustine, RT, and TMZ. These trials can be found on clinicaltrials.gov and are compiled in Table 2.

Lessons for the Future

There is an urgent need to improve outcomes of newly diagnosed GBM. A recent study that examined phase 3 GBM trials found that only 1 out of 11 trials in the past 25 years resulted in a prolongation of OS.[79] Possible explanations for this lack of success include the absence of molecular data, use of imaging criteria as a surrogate end point, lack of pharmacodynamic testing, improper selection of therapeutics warranting investigation, and need for improved design of phase 2 studies.[80]

Additionally, alternate approaches may be considered in improving local control outside the use of TMZ. A recent Adult Brain Tumor Consortium trial was a phase 1 study of the addition of veliparib, a poly(adenosine diphosphate ribose) polymerase inhibitor, to standard treatment. Though the results have been presented only in abstract form, the authors found the addition of veliparib to TMZ was too toxic because of hematologic toxicity.[81] Because the original Stupp trial showed a much smaller benefit of the addition of TMZ in MGMT-unmethylated patients as compared with MGMT-methylated patients,[82] this has led some to ask whether TMZ can be replaced with alternate agents. In the TMZ era, there is one published phase 2 trial using this approach, replacing TMZ with enzastaurin in patients with MGMT-unmethylated GBM. In a cohort of 57 patients, Wick et al[83] found that this regimen resulted in a median OS and PFS of 15 months and 6.6 months, respectively, and a 6-month PFS of 53.6%. Though this median OS is comparable to that of TMZ, the 6-month PFS missed the primary planned outcome of 55%. Twenty-six patients experienced grade 3 to 4 toxicities, 10 of which were thought to be possibly due to enzastaurin, and 7 patients died while on the study's drug therapy or within 30 days of discontinuation. Though not directly comparable, it is interesting to note that survival was worse when compared with the phase 2 trial that examined enzastaurin given alongside standard RT plus TMZ, and though grade 3 to 4 toxicity was rarer when omitting TMZ, serious adverse events were approximately the same.[24] The VERTU trial and Alliance N0877 trial are 2 randomized, phase 2 trials that have explored replacing TMZ with veliparib and dasatinib, respectively. However, results of these trials have been presented only in abstract form, with final results still awaiting publication.[84,85] It remains to be seen if the omission of TMZ represents a feasible strategy in radiosensitization of MGMT-unmethylated GBM.

Other strategies for improving local control with RT could employ techniques that were previously abandoned because of poor logistics or trial design. Beauchesne and colleagues used ultrafractionated RT 3 times per day of 0.75 Gy for 30 days in a cohort of newly diagnosed supratentorial GBM patients. The regimen was safe and well tolerated, with PFS and OS of 5.1 and 9.5 months, respectively.[86] This trial was initiated before TMZ became the standard of care, and the authors concluded ultrafractionated RT was superior to conventional RT alone but not RT plus TMZ. Outcomes for the phase 2 TEMOFRAC trial combining ultrafractionated RT and TMZ have been reported in abstract form only, with median survival not yet reached.[87] Alternatively, the promising outcomes of VPA with RT plus TMZ suggest agents not typically used for antitumor uses could be repurposed and investigated for effectiveness against GBM.

Good, reliable phase 2 data will be the key to determining successful agents to prolong life in patients diagnosed with GBM. The improved survival of TMZ in a phase 3 study was evident only after it had demonstrated promising survival outcomes in a phase 2 trial in which it was given both concomitantly with RT as well as adjuvantly in patients with newly diagnosed disease.[16] Comparatively, though phase 2 studies of bevacizumab had shown improved outcomes only in the setting of recurrent GBM, phase 2 research had demonstrated no improved OS in newly diagnosed patients.[88-90] Consequently, 2 large, randomized phase 3 trials found that although bevacizumab

improved PFS in the newly diagnosed setting, this did not translate into an OS benefit.[51,52]

Results reporting phase 2 trials for the development of radiosensitizers in patients with untreated GBM have been inconsistent (Table 1). Though OS is consistently reported, PFS is not. When PFS is reported, trials vary between reporting median PFS, 6-month PFS, or both. Part of this may be due to the difficulty in judging progression from pseudoprogression when central reporting is lacking.[20] Reporting of toxicity also lacks uniformity; most trials generally provide data on acute toxicity, but the reporting can be difficult to compare between trials. Some trials provide only the raw number of adverse toxicities, whereas others report the number of patients experiencing toxicities. Moreover, toxicities that are important in the assessment of radiosensitizers, such as late toxicity, variations in delivery of RT, and attribution of toxicity to RT or systemic agents, are almost never reported.

Though the addition of TMZ to standard adjuvant RT has significantly improved outcomes in GBM, prognosis remains poor. Local failure within the high-dose RT field emphasizes the need to optimize local treatment. There is a pressing need for additional therapies to improve the effectiveness of RT. Though there have been phase 2 trials of several radiosensitizers, few have advanced to phase 3 randomized trials. The lack of a control arm in many of these trials can make assessing their results unreliable.[21] Few of these trials have demonstrated improvement over historical standards, but it should be noted that many of these were undertaken without adequate preclinical data to justify the addition of the agent.[3] The promising results with newer agents developed with more robust preclinical data suggest that radiosensitization may still be a viable option in treatment of newly diagnosed GBM and warrants further investigation.

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