Recent developments in the treatment of high-grade gliomas

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Patients with glioblastoma and other high-grade gliomas have poor outcomes and are challenging to treat. The relative rarity of these tumors has made large-scale, practice-changing trials difficult to accomplish and has led to the formation of large multinational organizations that focus on neuro-oncology. This has resulted in the rapid completion of several large trials that in some cases have set new standards of care that can offer increased progression-free and overall survivals for some patients. The incorporation of correlative tissue studies in these trials has led to the identification of prognostic and predictive genetic markers that demonstrate the heterogeneity of these tumors and will assist in developing individualized treatment strategies as research continues to uncover new therapeutic targets. This review of recently completed and in-progress phase 3 trials in high-grade gliomas highlights the developments and future directions in the treatment of these tumors.

High-grade gliomas (HGG) are a diverse group of brain malignancies. Glioblastoma (GBM, WHO grade IV) is the most common of these gliomas and it accounts for more than half of all HGGs. The WHO grade III gliomas include anaplastic astrocytomas (AAs), anaplastic oligodendrogliomas (AOs), the mixed anaplastic oligoastrocytomas (AOAs), and the rarer anaplastic ependymomas and anaplastic gangliogliomas. Although malignant central nervous system (CNS) tumors comprise 1%-2% of all primary tumors in adults, they are responsible for the greatest loss of life with an average of 20 years of life lost per patient.[1,2] The treatment of these patients is challenging. In contrast to many systemic tumors, total resections are not possible and the blood-brain barrier limits the penetration of many chemotherapeutics. The presence of neurologic deficits and seizures as well as the medications used to treat these complications can have a significant impact on the patient's quality of life. Despite these hurdles, diagnostic and therapeutic advances have been made, and several large trials have recently completed or are underway (see Table). We review here several areas in which there is clinically relevant new data.

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Standard of care

Surgery is the initial treatment for patients with a grade III or IV glioma. In addition to providing material for a definitive tissue diagnosis, surgery alleviates symptomatic mass effect and can result in a reduced need for corticosteroids. Advances in surgical techniques and postoperative care have improved surgical outcomes and increased the ability to perform more complete resections safely, which for HGG associates with improved overall survival.[3] Postoperative external beam radiation is standard for HGG and as such, efforts have been made to improve efficacy. Highly conformal stereotactic radiosurgery has been evaluated in several large studies; in some the total dose delivered was raised from 60 cGy to 70 cGy, but none showed additional benefit over standard radiation.[4-6] Proton beam radiation is being explored as a therapy for HGG, although to date no studies have demonstrated increased efficacy or safety with its use. Proton therapy is usually restricted to tumors such as retinoblastoma or those near the base of the skull because of its ability to deliver a highly focused beam with minimal dosing to surrounding structures.

The current postsurgical standard of care for newly diagnosed GBM is based on the results of a randomized phase 3 study.[7] It demonstrated that focal radiation with daily concurrent temozolomide (TMZ, 75 mg/m^2) and postradiation TMZ (150-200 mg/m^2) for 5 days every 28 days (5/28 days) for up to 6 cycles resulted in a significant

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TABLE Recently completed and active phase 3 trials in high-grade glioma

RECENTLY COMPLETED

Drug(s), reference	Study population	Regimen (no. of patients)	mPFS, mo	mOS, mo	Comments
RT, PCV[14]	Newly diagnosed AO	RT (183) or RT→PCV (185)	RT: 13.21 RT→PCV: 24.3 HR, 0.66 [95% CI 0.52, 0.83]	RT: 30.6 RT→PCV: 42.6 HR, 0.75 [95% CI 0.60, 0.95]	Patients with 1p/19q codeletion benefit most from addition of PCV
PCV, RT[15]	Newly diagnosed anaplastic AO	RT (143) or PCV→RT (148)	RT: 1.7 years PCV→RT: 2.5 years (P = .003)	1p/19q codeleted: RT (n = 67): 7.3 years PCV→RT (n = 59) 14.7 years (P = .03)	
chemoRT and adjuvant TMZ[30]	Newly diagnosed GBM	Post TMZ/RT: 5/28 days TMZ (150-200 mg/m^2) or 21/28 days TMZ (75-100 mg/m^2) for 6-12 cycles (833)	5/28 days: 5.5 21/28 days 6.7 (P = .06)	5/28 days: 16.6 21/28 days: 14.9 (P = .63)	
RT or TMZ[24]	Newly diagnosed elderly anaplastic glioma or GBM, > 65 years	7 on/7 off TMZ (100 mg/m^2) (195) or RT (178)	Methylated MGMT: TMZ: 8.4 RT: 4.6 [95% CI 5.5-11.7 vs 4.2-5.0]	TMZ: 8.6 RT: 9.6 no SD HR, 1.09 [95% CI 0.84, 1.42], P noninferiority = .033	
Enzastaurin or Lomustine[24]	Recurrent GBM	Enzastaurin (174) or Lomustine (92)	Enzastaurin: 1.5 Lomustine: 1.6 P = .08	Enzastaurin: 6.6 Lomustine: 7.1 P = .13	An oral serine/threonine kinase inhibitor, targets protein kinase C and PI3K/AKT pathways
Cediranib[31]	Recurrent GBM	Cediranib (131) or Cediranib + lomustine (129) or lomustine (65)	Cediranib: 16% Cediranib + lomustine: 34.5% Lomustine: 24.5% no SD	Cediranib: 92 days (P = .889) Cediranib + lomustine 125 days (P = .162) Lomustine: 82 days	Anti-angiogenic VEGF inhibitor

ACTIVE PHASE 3 STUDIES

Drug(s), reference	Study population (approx. no. of patients)	Regimen	Comments
Cilengtide[32]	Newly diagnosed GBM, MGMT methylated(~ 504)	Cilengitide + TMZ/RT→TMZ compared with TMZ/RT→TMZ	
Bevacizumab[33]	Newly diagnosed GBM (~920)	TMZ/RT + biweekly BEV or placebo→TMZ + biweekly BEV or placebo	Accrual complete, initial data reports significant increase in PFS in BEV arm
Bevacizumab[34]	Newly diagnosed GBM (~942)	TMZ/RT + biweekly BEV or placebo starting week 4 of TMZ/RT→TMZ + biweekly BEV or placebo	
Low dose RT, TMZ[35]	Newly diagnosed elderly GBM ≥ 65 years (~560)	RT 40Gy in 15 doses or RT 40Gy in 15 RT + concurrent TMZ→TMZ	
Rindopepimut[36]	Newly diagnosed GBM, EGFRvIII + tumors (~440)	After TMZ/RT, TMZ +/− rindopepimut or placebo	Small peptide vaccine targeting EGFRvIII mutation found in 20%-30% of all primary GBM
dcVAX[37]	Newly diagnosed GBM (~300)	After TMZ/RT, TMZ +/− dcVAX or placebo over 24 mo; subjects in placebo arm can cross over at progression	Dendritic cells loaded with tumor lysate or placebo
NovoTTF-100A device[38]	Newly diagnosed GBM (~700)	After TMZ/RT, TMZ+/− continuously daily treatment with the NovoTTF-100A device	Delivers alternating electrical fields to tumor
TMZ/RT[39]	Newly diagnosed anaplastic gliomas without 1p/19q codeletions (~1360)	RT vs TMZ/RT vs RT→TMZ vs TMZ/RT→TMZ	
TMZ/RT[40]	Newly diagnosed anaplastic gliomas with 1p/19q codeletions (~488)	RT vs TMZ/RT vs TMZ/RT→RT	RT only arm to be dropped or changed in light of data demonstrating inferiority of RT alone compared with RT + chemo[14,15]

Abbreviations: AO, anaplastic oligodendroglioma; BEV, bevacizumab; EGFRvIII, epidermal growth factor receptor vIII (mutated variant of EGFR); GBM, glioblastoma; HR, hazard ratio; mo, month(s); mOS, median overall survival; mPFS, median progression free survival; no SD, no significant difference; PCV, procarbazine, lomustine, vincristine; RT, radiation therapy; TMZ, temozolomide; TMZ/RT, concurrent radiation and temozolomide; TMZ/RT→TMZ, concurrent radiation and temozolomide followed by adjuvant temozolomide; VEGF, vascular endothelial growth factor.

increase in overall survival (OS) of 14.6 months, compared with an OS of 12.1 months ($P < .001$) for patients who received only radiation. At 2 years, 26.5% of patients who received the combination regimen were alive, compared with 10.4% of those who received radiation only. Moreover, in a recent update, 9.8% of patients treated with the combination regimen were alive at 5 years, compared with 1.9% of those treated with radiation only.[8] This trial also demonstrated a relationship between clinical outcome and tumor levels of the DNA repair enzyme, O6-methylguanine-DNA methyltransferase (MGMT).[9] MGMT levels were indirectly determined by analysis of MGMT promoter methylation, an epigenetic change that silences gene transcription. Patients who received TMZ and whose tumors showed methylated MGMT promoters had a statistically significant improvement in median OS and in 2- and 5-year survival rates compared with patients with nonmethylated MGMT promoters.[8]

An evaluation of MGMT promoter status is now routinely incorporated into clinical trials with the aim of developing treatment approaches that are specific for methylated or nonmethylated tumors. A recent study, RTOG 0525, was based on data suggesting that prolonged exposure to TMZ depleted cellular MGMT levels and thus would theoretically sensitize nonmethylated tumors to TMZ. After initial resection for a GBM and completion of radiation with concurrent and adjuvant TMZ, patients were randomized to up to 12 monthly cycles of standard 5-day TMZ or to TMZ dosing of 21 days with 7 days off at 75-100 mg/m^2. The final results confirmed that MGMT status was associated with outcome.[10] However, when the standard and the experimental dosing arms were compared, there was no significant difference in OS (16.6 vs 14.9 months; $P = .63$) or median progression-free survival (PFS; 5.5 vs 6.7 months; $P = .06$). Patients in the experimental arm also had more grade 3 or 4 episodes of lymphopenia and fatigue. These phase 3 data do not support a change in the standard 5/28 days dosing regimen and do not support continued use of TMZ beyond 6 adjuvant cycles.

Improving the standard of care

Since the incorporation of TMZ in the initial treatment of GBM, numerous trials have added a diversity of novel agents to the regimen and several have shown promise by yielding OSs of 17 to 21 months. In fact, the rapid accumulation of potentially effective agents has raised the issue of whether it was the agents that were effective or if changes in practice patterns (eg, the more recent use of bevacizumab at recurrence) had resulted in a shift of the survival curves.[11] None of these agents (eg, talampanel, poly ICLC, vandetanib, cilengitide, among others) have entered into standard clinical care although they are under evaluation in phase 3 studies (Table). These include bevacizumab and the NovoTTF-100A device, which have both been approved by the Food and Drug Administration for the treatment of recurrent HGG, and the experimental agents, cilengitide, an integrin inhibitor; cediranib, an antiangiogenic agent; rindopepimut, a small peptide vaccine targeting the EGFRvIII (epidermal growth factor receptor vIII) mutation commonly found in GBM; and DCVax-L, a tumor-lysate−loaded dendritic cell vaccine.

Anaplastic oligodendrogliomas

The observation that AOs often showed response to chemotherapy and that response and improved outcomes were associated with the codeletion of chromosome arms 1p and 19q, led to 2 large prospective phase 3 trials, RTOG 9402 and EORTC 26951. The initial results were published in 2006 after a follow-up of at least 3 years.[12,13] The results showed no overall survival benefit when chemotherapy (a combination of procarbazine, lomustine, and vincristine; PCV) was added either before or after radiation in the upfront treatment of AO. Both studies demonstrated a difference in the time to tumor progression that strongly favored patients who received chemotherapy. The use of PCV was associated with a significant rate of hematological toxicity, with grade 3 or 4 toxicity reported in up to 65% of patients. Because of the uncertain benefits and added toxicity of PCV, neither of these regimens became a generally accepted standard of care.

The studies did however validate the prognostic value of 1p19q codeletion. For example, in RTOG 9402, patients with 1p19q codeletion had median survival times of 7 years, compared with less than 3 years for those without the codeletion ($P \leq .001$). Although neither study had a chemotherapy-only arm, the results led some practitioners to delay radiation until progression in patients with AO and 1p19q codeletion to avoid the late cognitive effects associated with radiation. In contrast, the poor survival outcomes for patients with nondeleted tumors led some practitioners to treat these patients with radiation and the TMZ regimen used for GBM.

Neuro-oncologists are being forced to reconsider these approaches in light of recently presented data derived from updated analysis of these trials.[14,15] For example, now with a median follow-up of 11.3 years, RTOG 9402 data shows that the OS of patients with 1p19q codeletions who received neoadjuvant chemotherapy was significantly longer (14.7 years), compared with those who received only radiation (7.3 years, $P = .03$). In contrast, the addition of chemotherapy to radiation had no impact

on the OS of patients with nondeleted tumors (2.6 vs 2.7 years, $P = .39$). Similar data were found for EORTC 26951 in which PCV was given after radiation. These data strongly support a new standard of care for 1p19q codeleted AO. The question that is most often asked is whether TMZ can substitute for the more toxic PCV regimen. This data may be forthcoming from a phase 3 study of patients who have newly diagnosed AA, AO, or AO with 1p19q codeletion (RTOG 1071), which opened before the new analyses of RTOG 9404 and EORTC 26951 were completed. Patients with anaplastic gliomas were to be randomized after surgery to radiation and TMZ with adjuvant TMZ, or radiation alone, or TMZ alone. The study was put on hold after the new RTOG 9404 and EORTC 26951 data demonstrated the inferiority of the radiation-only arm. The investigators are considering whether they should reopen the study with a PCV plus radiation arm, in which case the study would address whether TMZ can substitute for PCV.

Clearly, patients with anaplastic tumors without 1p19q codeletions have poor outcomes that approach those of GBM. It is not clear if these patients actually derive any benefit from being treated with the GBM radiation/TMZ regimen even though it is widely used in this population. The CATNON (Chemoradiation and Adjuvant Temozolomide in Nondeleted anaplastic tumors) study is addressing how to approach these patients. This randomized study has 4 arms: radiation only, or radiation and concurrent TMZ, or radiation followed by TMZ for up to 12 cycles, or radiation with concurrent and adjuvant TMZ for up to 12 cycles. The trial end point is OS, and the study is designed to allow stratification of outcome by MGMT promoter status.

Antiangiogenic agents

Malignant gliomas are highly vascular and stimulate angiogenesis through the secretion of vascular endothelial growth factor (VEGF) that induces endothelial cell growth.[16] Many tumor vessels have endothelial gaps that contribute to peritumoral edema. Antiangiogenic agents such as bevacizumab are therefore appealing for the treatment of malignant gliomas. Theoretically, antiangiogenic drugs would not only disrupt the proangiogenic pathways that support tumor growth and invasion but they could have an impact on edema. There is also data to suggest that antiangiogenic agents normalize tumor vasculature that could improve blood flow efficiency resulting in improved drug and oxygen delivery.

The accelerated approval of bevacizumab for the treatment of recurrent HGG in the United States was based on the findings of 2 uncontrolled phase 2 studies that evaluated bevacizumab as a single agent or in combination with irinotecan.[17,18] These studies reported overall response rates from 19.6% to 28% for single-agent bevacizumab, PFS at 6 months (PSF-6) ranging from 29% to 42.6%, a median OS ranging from 31 to 36 weeks, and median duration of responses ranging from 3.9 to 4.2 months. Bevacizumab has not been approved by the European Medicines Agency amid concerns that the studies were not controlled and that questions remain regarding efficacy, dosing, and schedule.

The currently approved schedule for recurrent HGG is 10 mg/kg every 2 weeks until progression or toxicity. This schedule was selected in large part because of the irinotecan-dosing schedule used in the combination study noted above. Small noncontrolled studies suggest that other dosing schedules such as 5 mg/kg every 2 weeks or 15 mg/kg every 3 weeks produce similar results, although this has not formally been tested.[19,20]

Although approved as a single agent, it is not uncommon for practitioners to combine bevacizumab with other agents, and many agents have been assessed in phase 2 trials (eg, temsirolimus, carboplatin, lomustine, carmustine, fotemustine, erlotinib, etoposide, and enzastaurin). None of these drugs appear to increase clinical benefit while they are often associated with increasing rates of grade 3 and 4 adverse events. At this time, it seems unjustified to combine agents with bevacizumab outside of a clinical trial.

New response criteria

The response of gliomas to antiangiogenic agents may be rapid and dramatic and is often associated with a reduced requirement for corticosteroids. The rapid reduction in contrast enhancement that could be mistaken for tumor response is not primarily because of cytotoxic activity but rather because of decreased permeability of the tumor vessels.[21] In contrast, 20% to 30% of patients with newly diagnosed GBM who are receiving radiation and TMZ develop increasing or new contrast enhancement and edema early in treatment that is not a result of tumor progression (Figure). This process, called pseudoprogression, most often occurs within 3 months of radiation and TMZ and is often associated with clinical worsening, a need for re-institution, or increase of corticosteroids, and occasionally re-operation.[22] The changes are likely a result of treatment-related injury and the breakdown of the blood-brain barrier. Thus, the use of two-dimensional measurements of the tumor on contrast-enhanced CT or MRI that has been the mainstay of determining glioma response in clinical trials and general practice has clearly become inadequate.

To address this shortcoming, the Response Assessment in Neuro-Oncology Working Group has developed

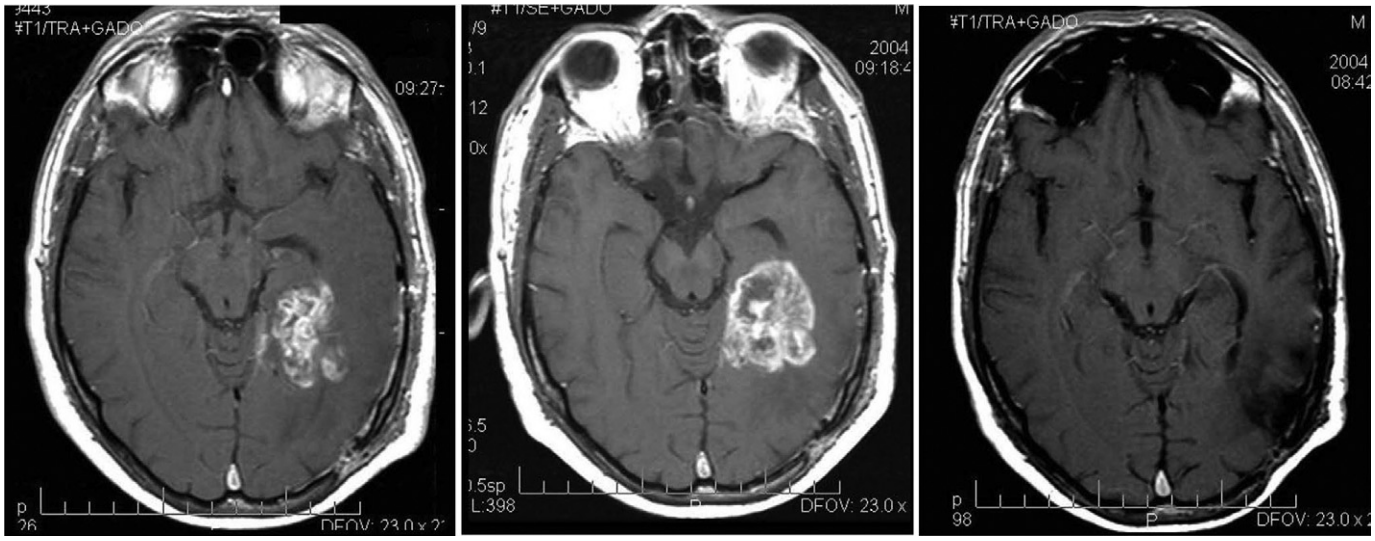

FIGURE Pseudoprogression after radiation with concurrent and adjuvant TMZ. A 65-year-old man who was diagnosed with a left frontal GBM underwent a gross total resection followed by 6 weeks of radiation with concurrent TMZ. From left to right: T1-weighted MRI with contrast after resection showing postsurgical changes; T1-weighted MRI with contrast after completion of radiation and TMZ showing increased contrast enhancement (center image); and T1-weighted MRI with contrast after completion of 6 cycles of adjuvant TMZ showing complete resolution of contrast enhancement supporting post-treatment changes as consistent with pseudoprogression.

new brain tumor response criteria.[23] An important component of the criteria that is particularly relevant to patients receiving antiangiogenic agents is the inclusion of the measurement of the nonenhanced tumor best seen on T2-weighted fluid-attenuated inversion recovery MRI sequences. In addition, because of the difficulty in differentiating tumor progression from pseudoprogression in patients who are receiving radiation and TMZ, it is recommended that no determination of treatment failure be made in the 3 months after radiation and TMZ unless the progression is clearly outside the radiation field (defined as beyond the 80% isodose line).

Bevacizumab and newly diagnosed glioblastoma

Considering the highly vascular nature of gliomas, soon after the FDA's approval of bevacizumab for recurrent HGG investigators asked whether the use of bevacizumab at initial treatment would be advantageous. In one study, outcomes in patients who received early bevacizumab were compared with outcomes in a control group in which patients received bevacizumab at recurrence after initial radiation and TMZ. There was no difference in OS (19.6 months vs 21.1 months, respectively, $P < .06$), but there was a significant increase in PFS (13.6 months vs 7.6 months, $P < .005$), which suggested that timing of bevacizumab therapy may not be critical for it to have an impact on OS. Considering that the study used contrast-enhancement–based imaging criteria of response, in retrospect the increase in PFS should be interpreted with caution. Subgroup analysis suggested that patients with poor prognostic factors may have had more benefit from early bevacizumab. This could be explained in part by the ability of bevacizumab to decrease edema and reduce the need for corticosteroids that are associated with complications that contribute to morbidity and mortality.

A definitive answer to the question of a potential benefit of upfront bevacizumab will likely be forthcoming with the future completion of 2 large randomized phase III trials. RTOG 0825 and the AVAglio study (with enrollment completed) evaluate the efficacy of bevacizumab added to standard radiation with concurrent and adjuvant TMZ in the upfront treatment of GBM. The sponsor of the AVAglio study, Roche, recently announced that the study shows an increase in PFS-6 with the addition of bevacizumab; results for OS are pending in 2013.

Treatment of elderly patients with high-grade gliomas

The incidence of GBM increases with age and about half of all cases occur in patients over the age of 65 years. Surveys and epidemiological studies show that elderly HGG patients have worse outcomes than do younger patients. The reasons for this are likely multifactorial and include the prevalence of medical comorbidities with poly-pharmacy in elderly patients, which leads to toxicity or decreased efficacy of tumor-targeted therapeutics; intrinsic genetic differences in the tumors in the elderly; and less aggressive therapy.

For GBM patients over the age of 70 years, standard external beam radiation consisting of a total dose of 60 Gy delivered in 30 fractions of 2 Gy has been shown to be superior to best supportive care and is most commonly the only treatment elderly patients receive. Other schedules including daily doses of 3 Gy in 15 fractions or lower total doses have been studied and likely have equal efficacy and toxicity. However, radiation is often not well tolerated in the elderly. Patients often develop fatigue and/or nausea and can require increased or prolonged use of corticosteroids, which result in hyperglycemia and myopathy. The development of new approaches for this population has been slow because elderly patients have largely been excluded from clinical trials, including the 2005 trial that set the standard of care for newly diagnosed GBM patients.[7]

The favorable toxicity profile of TMZ has led to several studies in which TMZ (most commonly dosed 150 mg to 200 mg/m^2 on the 5/28 days dosing regimen) was substituted for postoperative radiation. Median survivals from 5 to 6 months were similar to those obtained with radiation, and TMZ was well tolerated. In a recently published phase 3 trial, patients older than 65 years with GBM were randomized to TMZ at 100 mg/m^2, 7 days on alternating with 7 days off, or to standard radiation at 60 Gy administered over 6-7 weeks. The results demonstrated that TMZ was not inferior to radiation, with the median OS at 9.6 months in the radiation-only arm, compared with 8.6 months in the TMZ arm (hazard ratio [HR], 1.09; 95% CI, 0.84-1.42; $P = .033$).[24] Of particular note, older patients with methylated MGMT promoters had longer event-free survival (EFS) if they received TMZ, whereas those without promoter methylation had longer EFS if they received radiation, suggesting that MGMT status in this population can guide treatment choices. It remains untested whether or not radiation with concurrent and/or adjuvant TMZ in the elderly would be superior to either TMZ or radiation alone. An ongoing study (NCT00482677/EORTC26062/NCIC-CE6 trial) that will randomize older patients to a short course of radiation (40 Gy over 15 days) or a short course of radiation with concurrent and adjuvant TMZ will address this question albeit with a different radiation schedule.

As with younger patients, there are few effective options for any patient with HGG at recurrence. Radiation is a reasonable choice for an elderly patient who may have received only TMZ upfront, although that has not been formally studied. Bevacizumab is tolerated by older patients and if performance status and other medical conditions allow another option. It is interesting to note that findings in a recent retrospective study suggest that not only do older patients tolerate bevacizumab, they may have increased benefit over younger patients (age separation, < 55 or ≥ 55 years). Patients older than 55 years and with poor Karnofsky performance status (< 80) had significantly better PFS when they were treated with bevacizumab compared to a historical control group of older patients who received treatments other than bevacizumab.[25] The older bevacizumab-treated patients also had significantly longer OS. The demonstration that the tumors of the older patients had higher levels of VEGF than the younger cohort may partially explain these findings.

New molecular markers

The presence of 1p19q codeletion is associated with more favorable prognosis of oligodendroglial tumors and MGMT promotor methylation seems to predict better outcome in patients with GBM who are treated with alkylating agents. The identification of additional markers will improve the ability to stratify patients for clinical trials that will result in individualized therapeutic approaches. Recently, it has been found that 70% of low-grade and anaplastic gliomas and secondary GBM (those that arise from lower-grade tumors and representing about 5% of all GBM) harbor mutations of the isocitrate dehydrogenase gene (IDH1, and to a much lesser extent IDH2). The presence of IDH1 mutations in these tumors is a favorable prognostic factor. Subsequent studies have shown that IDH1 mutation is predictive of response to TMZ in patients with low-grade gliomas.[26] A randomized phase 3 study of patients with anaplastic gliomas who were treated with sequential radiation and PCV chemotherapy or the reverse found that IDH1 mutation had a favorable impact on outcome that was stronger than codeletion of 1p19q or MGMT promoter methylation.[27] IDH1 mutations are almost never found in tumors of older patients which may in part explain the poorer outcome of this population.[28,29]

These and other studies clearly support the strong positive prognostic value of IDH1 mutation, whereas its predictive value remains to be clarified. In addition to its prognostic value, mutant IDH provides yet another potential therapeutic target.

Conclusion

The increased recognition of molecular subgroups of glioma, the identification of new predictive and prognostic markers, and the increasing availability of targeted biologic agents have resulted in a surge of new clinical trials. As with systemic cancers, identification of populations more likely to respond to a specific targeted agent will hopefully yield individualized therapeutic approaches with improved outcomes. However, answers will not be

forthcoming unless patients enroll in clinical trials and practitioners are encouraged to refer patients to centers where trials are available.

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