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Current Standards of Care in Glioblastoma Therapy

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Abstract: Glioblastoma (GBM) is the most common primary malignant brain tumor in adults. Regardless of ideal multidisciplinary treatment, including maximal surgical resection, followed by radiotherapy plus concomitant and maintenance temozolomide (TMZ), almost all patients experience tumor progression with nearly universal mortality and a median survival of less than 15 months. The addition of bevacizumab to standard treatment with TMZ revealed no increase in overall survival (OS) but improved progression-free survival (PFS). In newly diagnosed GBM, methylation of the O6-methylguanine-DNA methyltransferase (MGMT) promoter has been shown to predict response to alkylating agents, as well as prognosis. Therefore, MGMT promoter status may have a crucial role in the choice of single modality treatment in fragile elderly population. No standard of care is established in recurrent or progressive GBM. Treatment alternatives may include supportive care, surgery, re-irradiation, systemic therapies, and combined modality therapy. Despite numerous clinical trials, the identification of effective therapies is complex because of the lack of appropriate control arms, selection bias, small sample sizes, and disease heterogeneity. Tumor-treating fields plus TMZ represent a major advance in the field of GBM therapy, and should be

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considered for patients with newly diagnosed GBM with no contraindications. As a disease with such a poor prognosis, treatment of GBM should go beyond improving survival and aim at preserving and even improving the quality of life of both the patient and the caregiver.

Key words: Bevacizumab; Glioblastoma; MGMT; Radiotherapy; Temozolomide

Introduction

Glioblastoma (GBM) is the most common and devastating primary malignant brain tumor in adults, encompassing 16% of all primary brain and central nervous system neoplasms (1). Regardless of advanced diagnostic modalities and ideal multidisciplinary treatment that includes maximal surgical resection, followed by radiotherapy (RT) plus concomitant and maintenance temozolomide (TMZ) chemotherapy, almost all patients experience tumor progression with nearly universal mortality. The median survival from initial diagnosis is less than 15 months, with a 2-year survival rate of 26–33% (2, 3). The addition of bevacizumab to standard treatment revealed no increase in overall survival (OS), but improved progression-free survival (PFS). That finding caused considerable debate regarding whether the combination is cost-effective in first-line treatment (4, 5). In newly diagnosed GBM (nGBM), methylation of O6-methylguanine-DNA methyltransferase (MGMT) promoter has been shown to predict response to alkylating agents; its status may play a crucial role in the choice of single modality treatment in fragile elderly population (6–8).

Currently, no standard of care is established for recurrent or progressive GBM (rGBM) (9). Despite numerous clinical trials, the identification of effective therapies is complex due to the lack of appropriate control arms, selection bias, small sample size, and disease heterogeneity (10). Treatment alternatives may include supportive care, reoperation, re-irradiation, systemic therapies, and combined modality therapy. Therapeutic options need to be carefully weighted, taking into account tumor size and location, previous treatments, age, Karnofsky performance score (KPS), patterns of relapse, and prognostic factors. The association of tumor-treating fields (TTFields) with TMZ represents the first major advance in the field of GBM therapy in approximately a decade and should be considered for newly diagnosed patients with no contraindications (11). As a disease with such a poor prognosis, treatment of GBM should go beyond improving survival and aim at preserving and even improving the quality of life (QoL) of both the patient and the caregiver.

Newly Diagnosed Glioblastoma

SURGERY

Surgery is the initial therapeutic approach for GBM and remains a hallmark in the treatment of malignant brain tumors. Some preoperative issues such as medical conditions of the patient, appropriate imaging and functional studies,

neuropsychological evaluation, and the use of corticosteroid and antiepileptic drugs should be taken into account. While steroids can control cerebral edema and symptoms/signs of intracranial hypertension, thus improving brain conditions for surgical resection, antiepileptic drugs should not be used prophylactically (12). In patients with brain tumors who have not had a seizure, tapering and discontinuing anticonvulsants after the first postoperative week is appropriate (12). Attention should be paid to patients who are going to be operated with cortical stimulation, in an asleep–awake–asleep manner, due to the potential development of stimulation-induced seizures. The goals of surgical treatment are: maximal safe resection; tissue specimen for pathological diagnosis; improving conditions for complementary treatments; delaying clinical worsening; and improving QoL.

While strong predictors of good outcome are essentially patient related, the most important treatment-related predictor is extent of resection (EOR) (13). A more extensive surgical resection is associated with longer life expectancy, achieving the longest survival in those patients who undergo gross total resection followed by RT and TMZ (13–15). An important issue is the fine balance between the aggressive removal and the preservation of function; so the goal is to achieve maximal safe surgical resection. A postoperative magnetic resonance imaging (MRI) should assess the EOR within 72 h of surgery. MRI after 72 h of surgery cannot be relied upon because of inflammatory postoperative changes. It has been postulated that $\geq 98\%$ EOR is necessary to improve survival significantly (16). However, Sanai and colleagues showed that, for oncological purposes, resections of 78% of the tumor volume, associated with chemoradiotherapy, already have prognostic advantages (17). More recently, some authors revealed that more important than the EOR is the amount of the residual volume (18, 19).

Tumors located within eloquent cortex pose a particular surgical challenge due to the high risk of postoperative neurological deficits (20). Muller and colleagues, using functional MRI to map the functional cortex, showed that postoperative neurological deficits occurred in 0% of cases in which the resection margins were beyond 2 cm of the eloquent cortex, in 33% of cases when resection margins were within 1 to 2 cm, and in 50% of cases when resection margins were less than 1 cm (21). Intraoperative electrical stimulation mapping with awake craniotomy decreases the risk of novel neurological deficits, while maximizing the EOR (17, 22). A large meta-analysis demonstrated that resections with the use of intraoperative functional mapping were associated with fewer late severe neurological deficits (3.4% vs. 8.2%) and more extensive resection (75% vs. 58%), although the tumors were more frequently in eloquent locations (100% vs. 96%) (23). Motor evoked potentials and somatosensory evoked potentials can also be recorded during surgery to continuously monitor the integrity of motor and somatosensory pathways.

To increase the EOR, enhancing the visualization of the tumor margins, some fluorescent agents have been used, namely the most widely employed 5-aminolevulinic acid (5-ALA). Panciani and colleagues showed that fluorescence-guided resection revealed a sensitivity of 91.4% and a specificity of 89.2% (24). The use of 5-ALA increases the rate of gross total resection, in randomized controlled trials (65% vs. 35%) and in observational studies (from 25 to 94.3%) (25, 26), and also increases PFS (8.6 vs. 4.8 months) and the 6-month PFS (PFS6)

(46% vs. 28%) (27, 28). The increase in gross total resection rate and PFS was confirmed by three meta-analyses performed to evaluate the literature on 5-ALA. Fluorescein is another option but was not tested in randomized controlled trials (25). Fluorescence near eloquent areas should be managed carefully. A biopsy should be reserved for patients with multiple comorbidities, who would not be able to tolerate a large cranial surgery, or for those with unresectable tumors, and the only benefit is provision of tissue specimen for pathological diagnosis (29). The surgery also allows relieving of the mass effect with concurrent amelioration of symptoms, in patients with increased intracranial hypertension and brain edema, leading to an improvement in the QoL.

COMPLEMENTARY TREATMENT

The current standard of care for patients with nGBM is maximum safe surgical resection followed by concurrent TMZ (75 mg/m²/day for 6 weeks) and RT (60 Gy in 30 fractions) and then six maintenance cycles of TMZ (150–200 mg/m²/day for the first 5 days of a 28-day cycle—sdTMZ), according to the results of the phase III EORTC 26981 (2). Stupp et al. showed an OS and PFS improvement with the combination therapy relative to RT alone (median OS 14.6 vs. 12.1 months; $P < 0.001$) (3). These results were supported by other trials (30–33). A recently published meta-analysis by Feng et al. revealed a median OS of 13.4–19.0 months in the combination treatment group, as opposed to 7.7–17.1 months in the RT-alone group (34).

Age, neurological status (assessed by KPS and Mini Mental State Examination), EOR, IDH (isocitrate dehydrogenase) mutations, and methylation of the MGMT promoter region are established prognostic factors in GBM patients (35, 36). The predictive role of MGMT promoter methylation in response to TMZ has also been established in several studies (3, 37). Nevertheless, the clinical utility of MGMT remains poor, primarily because of a lack of therapeutic options for patients with unmethylated MGMT promoter GBM. The only exception is in the management of elderly patients with GBM. TMZ is an oral chemotherapeutic drug that induces DNA methylation and tumor cytotoxicity through cell cycle arrest. The cytotoxic activity of TMZ and other alkylating agents is apparent by the formation of O6-methylguanine DNA adducts, which are repaired by the enzyme MGMT. Consequently, the primary mechanism of resistance to TMZ is dependent on the MGMT activity (38). It exhibits a linear pharmacokinetics with excellent bioavailability, readily enters the cerebrospinal fluid, and it does not require hepatic metabolism for activation (39). Although evidence suggests that TMZ chemotherapy is associated with few adverse events, risk of hematological complications, fatigue, and infections were increased with its use (40).

DOSE-DENSE TEMOZOLOMIDE

Dose-dense schedules of TMZ (ddTMZ) have been designed to deplete tumor MGMT levels and thereby improve activity of TMZ, particularly in the MGMT unmethylated GBM cohort (41). In the RTOG 0525 phase III trial, 833 patients were randomized to receive sdTMZ or ddTMZ (75–100 mg/m² days 1 through

21 of a 28-day cycle), for 6–12 cycles, after completion of concomitant RT-TMZ. The median OS (16.6 vs. 14.9 months; $P = 0.63$) and the median PFS (5.5 vs. 6.7 months; $P = 0.06$) were not significantly different between the two treatment arms. There was increased grade ≥ 3 toxicity in ddTMZ arm (34% vs. 53%; $P < 0.001$), as well as a greater deterioration on function subscales and QoL (2).

DURATION OF TEMOZOLOMIDE MAINTENANCE THERAPY

RT with concomitant and adjuvant TMZ was initially introduced with six TMZ maintenance cycles (3). In clinical practice, however, many centers continue TMZ therapy beyond six cycles. The impact of this strategy is controversial and has not yet been confirmed in prospective randomized clinical trials. A phase II comparison of 6 versus 12 cycles of TMZ (NCT02209948) is currently underway. Some retrospective studies suggested a benefit in OS with extension of maintenance TMZ (42–45). The major limitation of all these studies, beyond the retrospective nature, is the comparison of patients who were treated with at least seven cycles of TMZ to patients receiving ≤ 6 cycles, who, in most cases, stopped TMZ because of tumor progression. Other limitations are missing information on MGMT methylation and univariate Kaplan–Meier description of OS, but no investigation of significance by multivariate Cox regression (42–45). Data from a large pooled analysis of four clinical trials for nGBM indicates that extended treatment with TMZ beyond six cycles is not associated with improved OS, but prolongs PFS (2, 3, 46–48). A similar analysis was performed in patients enrolled in the German Glioma Network. A total of 61 of the 142 identified patients received at least seven maintenance TMZ cycles (median 11, range 7–20). Patients with extended maintenance TMZ treatment had better PFS (20.5 months vs. 17.2 months; $P = 0.035$) but not OS (32.6 months vs. 33.2 months; $P = 0.126$). However, there was no significant association of prolonged TMZ chemotherapy with PFS or OS adjusted for age, EOR, KPS, presence of residual tumor, MGMT promoter methylation status, or IDH mutation status (49). This study provides Class III evidence that in patients with nGBM, prolonged TMZ chemotherapy does not significantly increase PFS or OS.

GLIADEL (CARMUSTINE) IMPLANTABLE WAFERS

Biodegradable carmustine wafers, implanted into the tumor bed, after near or complete tumor resection, has been approved by the FDA for first-line treatment of GBM and anaplastic glioma. Nevertheless, the use of carmustine wafers remains controversial due to the questionable survival benefit and potential adverse events (50).

OPTIMAL DOSE-FRACTIONATION SCHEDULE FOR EXTERNAL BEAM RADIATION THERAPY

For patients aged under 70 years with good PS ($KPS \geq 60$), the optimal dose-fractionation schedule for external beam RT, following resection or biopsy, is 60 Gy in 2 Gy fractions delivered over 6 weeks. Numerous other dose schedules have been explored without clear benefits. Attention must be paid to ensure that

dose to critical structures (such as brainstem, optic chiasm, optic nerves) is kept within acceptable limits. Risk of radiation necrosis increases with concurrent chemotherapy and larger volume of irradiated brain. The QUANTEC authors emphasize that for most brain tumors, there is no clinical indication to give fractionated RT > 60 Gy (51).

TARGETED THERAPY—IS THERE A PLACE IN NEWLY DIAGNOSED GLIOBLASTOMA?

Since GBM is one of the most vascularized tumors, antiangiogenic therapeutic strategies are very attractive. Bevacizumab is a monoclonal antibody that binds to circulating VEGF-A and inhibits its biological activity by preventing the interaction with the VEGF receptor. This leads to a reduction in endothelial proliferation and vascular growth within the tumor (52). Bevacizumab was approved by the FDA, based on unprecedented response rates (RRs) in rGBM, which led to its evaluation in the postoperative setting of nGBM (Table 1) (64, 65). Two large phase III, randomized, placebo-controlled trials, adding bevacizumab to standard treatment were conducted (4, 5). In the RTOG 0825 trial, median PFS was increased (10.7 vs. 7.3 months), although it did not reach the predefined significance level, and there was no difference in OS between the two treatment groups. The MGMT methylation status and recursive partitioning analysis (RPA) class were prognostic regardless of the study treatment. A decline in QoL and neurocognitive function (NCF) was more frequently observed with bevacizumab (5). In the AVAglio trial, there was a significant increase in PFS (10.6 vs. 6.2 months; $P < 0.001$), but not in OS. Baseline health-related QoL and PS were maintained longer in the bevacizumab group (4). Grade 3 or 4 toxicities occurred more often in the bevacizumab arms of both studies. In RTOG 0825, the crossover from placebo to bevacizumab, at disease progression, was planned and occurred in 48.3% of patients, and in AVAglio, the crossover was about 30%. This may have eliminated a potential survival benefit (4, 5). In both RTOG 0825 and AVAglio, efforts have been made to identify a subset of patients who could benefit from upfront treatment with bevacizumab, but no marker proved consistently effective in predicting either response or resistance to bevacizumab (4, 5).

In summary, these trials have shown that the combination of bevacizumab with standard RT–TMZ for the treatment of nGBM resulted in improved median PFS, without gain in OS. Data regarding QoL and functional status are contradictory. Not surprisingly, there was an increase in adverse events associated with bevacizumab therapy. Cilengitide, a selective $\alpha v\beta 3$ - $\alpha v\beta 5$ -integrin inhibitor, had shown promising results in phase II trials, with more pronounced benefits in GBM with methylated MGMT promoter (66–68). Two prospective randomized trials evaluated the role of cilengitide in combination with standard treatment, in patients with a methylated MGMT gene promoter (CENTRIC) and in those with an unmethylated MGMT status (CORE). They both failed in demonstrating an OS gain (47, 48). Other agents, namely enzastaurin and temsirolimus, have been studied in phase II trials, without any improvement in OS or PFS (41).

TABLE 1 Clinical trials with bevacizumab in the newly diagnosed glioblastoma

Reference	Arm 1	Arm 2	Phase	n	RR (%)		PFS6 (%)		OS (months)	
					Arm 1 versus Arm 2	Arm 1 versus Arm 2	Arm 1 versus Arm 2	Arm 1 versus Arm 2		
RTOG 0825 trial (5)	BVZ/TMZ + RT → TMZ/BVZ	Placebo/TMZ + RT → TMZ/placebo	III	637	-	10.7 vs. 7.3 (<i>P</i> < 0.0007)	-	15.7 vs. 16.1 (<i>P</i> = 0.21)		
AVAglio trial (4)	BVZ/TMZ + RT → TMZ/BVZ	Placebo/TMZ + RT → TMZ/placebo	III	921	-	10.6 vs. 6.2 (<i>P</i> < 0.001)	-	16.8 vs. 16.7 (<i>P</i> = 0.10)		
(53, 54)	BVZ + RT → BVZ/IRI	TMZ + RT ⊕ TMZ	III (MGMT-nonmethylated)	171	-	9.7 vs. 5.9 (<i>P</i> = 0.0004)	80 vs. 41 (<i>P</i> < 0.0001)	16.6 vs. 17.3 (<i>P</i> = 0.9)		
(55)	BVZ/TMZ + hypo-IMRT → TMZ/BVZ	TMZ + hypo-IMRT → TMZ	II	56	-	12.8 vs. 9.4 (<i>P</i> = 0.58)	84 vs. 83 (<i>P</i> = 0.702)	16.3 in both		
(56)	BVZ/TMZ + hypo-RT → TMZ/BVZ	-	II	40	57	10	93 (1 year)	19		
(57)	TMZ + RT → TMZ/BVZ	-	II	62	-	8.8	-	16.5		
(58)	TMZ + RT → BVZ/EVE	-	II (MGMT-nonmethylated)	48	-	7.3	-	14.2		
(59)	BVZ/TMZ + RT → TMZ/BVZ	-	II	51	-	13.0	85.1	23.0		
(60)	BVZ/TMZ + RT → BVZ/EVE	-	II	68	61	11.3	-	13.9		
(61)	BVZ/TMZ + RT → TMZ/BVZ/TOP	-	II	80	-	11.1	-	17.2		
(62)	BVZ/TMZ + RT → TMZ/BVZ/IRI	-	II	75	-	14.2	-	21.2		
(63)	BVZ/TMZ + RT → TMZ/BVZ	-	II	70	-	13.6	88	19.6		

BVZ, bevacizumab; EVE, everolimus; hypo-IMRT, hypofractionated-intensity-modulated RT; IRI, irinotecan; OS, overall survival; PFS, progression-free survival; PFS6, 6-month PFS; RR, Response Rate; RT, radiotherapy; TMZ, temozolomide; TOP, topotecan.

Recurrent Glioblastoma

SURGERY AT RECURRENCE

When tumor recurs, treatment options include supportive care, reoperation, re-irradiation, systemic therapies, and combined modality therapy. In this setting, the role of reoperation remains unclear. A recent review of the literature, including 28 studies and 2279 patients, who underwent second surgery, showed a median survival from reoperation of 9.7 months and concluded that EOR at reoperation improves OS, even in patients with subtotal resection at initial surgery (69). Nonetheless, clinical and survival benefit is dependent on patient and tumor characteristics, which need to be considered before pursuing a second surgery. The most consistently demonstrated prognostic factor is favorable PS (KPS ≥ 70), which associates with significantly improved PFS and OS, following salvage therapy (70–76). Younger age is the second most frequently reported prognostic factor associated with improved survival (70, 72, 77, 78). Park et al. have devised a scale to predict survival after reoperation based on tumor involvement of pre-specified eloquent/critical brain regions (MSM, motor–speech–middle cerebral artery score), KPS score of 80, and tumor volume (50 cm^3). The scale identified three statistically distinct groups within the validation cohort as well (median survival of 9.2, 6.3, and 1.9 months, respectively) (76). Recently, a new 3-tier scale was developed, including KPS score of 70 and ependymal involvement, allowing identification of groups of patients with significant differences in median OS after reoperation (79). Maximal tumor volume resection should be the surgical goal even in candidates for a second surgery. In this perspective, involvement of eloquent brain usually precludes this objective and is associated with shorter OS (15, 80). Molecular markers' impact in rGBM is still a matter of debate. Brandes et al. reported that MGMT methylation status determined at first surgery seems to be of prognostic value, although it is not predictive of outcome after the second surgery (81).

The DIRECTOR trial, although not aimed at addressing the reoperation issue, allowed the retrospective analysis of EOR and residual tumor volume in approximately two-thirds of the patients, who underwent surgery prior to study entry. Complete resection of enhancing tumor was achieved in 68% of the patients, and in multivariate analysis it was found to be an independent predictor for post-resection survival (82). A multicenter retrospective study, including 503 patients with rGBM submitted to reoperation, concluded that preoperative and postoperative KPS, EOR of first re-resection, and chemotherapy after first re-resection significantly influenced survival after reoperation. Importantly, this study reported a rate of permanent new deficits after first re-resection of 8% (83). In conclusion, evidence suggests higher OS in selected patients who undergo reoperation at the time of GBM recurrence. It should be considered in patients with a good KPS and a favorable preoperative clinical and radiological characteristics. Age <60 years and KPS ≥ 70 are particularly associated with better outcome. Of paramount importance are the preservation of eloquent brain areas and the avoidance of neurological deterioration after second surgery, since that might mitigate the expected survival benefit.

RE-IRRADIATION AND SPECIAL TECHNIQUES

The majority of studies on re-irradiation of gliomas are retrospective and they use a variety of techniques, including brachytherapy, fractionated stereotactic RT (FSRT), radiosurgery, and conformal or intensity-modulated RT, with or without new systemic agents. Furthermore, the published data include a wide range of doses, emphasizing the fact that no standard approach exists (84). Inter-study comparison is difficult because studies have heterogeneous samples, different endpoints, and some patients were treated at first and others at second or third progression. Although the biology of re-irradiation remains to be fully understood, there is now a large body of clinical and animal data that can guide recommendations. Mayer and Sminia identified and analyzed 21 studies on re-irradiation of gliomas (85). They opined that the incidence of toxicity, including radionecrosis, may be underreported, since only symptomatic necrosis is likely to be recorded. The major factor contributing to necrosis was the total dose received. There was no correlation between time to re-irradiation and its development, although the minimum time interval between treatments was 3 months. They concluded that the incidence of necrosis did not increase significantly until the total cumulative dose was 100 Gy. In younger patients with good PS, focal re-irradiation (stereotactic radiosurgery, SRS; hypofractionated stereotactic radiotherapy, HFSRT) for rGBM may improve outcomes compared to supportive care or systemic therapy alone. Tumor size and location should be taken in to account, when evaluating safety of re-irradiation.

STEREOTACTIC RADIOSURGERY AND HYPOFRACTIONATED STEREOTACTIC RADIOTHERAPY

Since most recurrences occur within brains previously irradiated with a high dose, re-irradiation with doses and margins used in the primary treatment of GBM could confer high toxicity risks. Thus, limited volume re-irradiation using SRS or HFSRT is often employed. Stereotactic methods offer optimal precision of target definition while sparing dose to the surrounding tissues. Both SRS and HFSRT deliver more than 2 Gy per fraction and typically have smaller margins and much shorter durations than conventionally fractionated radiotherapy (cfRT). RTOG 90-05, a phase I dose escalation study, established maximum tolerated doses and demonstrated that single-fraction SRS could be performed, in this setting, with acceptable morbidity (86). In the rare event that disease recurs in a portion of brain not previously irradiated, cfRT with chemotherapy should be considered, after surgery.

SRS and HFSRT appear to provide promising outcomes compared to chemotherapy alone for the treatment of rGBM. Shepherd et al. described 29 recurrent high-grade glioma patients treated with a diversity of HFSRT doses with a median OS of 11 months (87). This compared favorably to a matched cohort of patients treated with nitrosourea chemotherapy, with a median OS of 7 months. The studies were nearly all retrospective, however, lacking randomized control groups and with inherent selection bias limiting conclusions. Several of the early studies involving single-fraction SRS reported high rates of radiation necrosis requiring

reoperation (20–40%) (86, 88–90). Compared to SRS, the use of HFSRT may help to mitigate the risk of adverse radiation events. A series of 105 GBM patients treated with 35 Gy in 10 fractions had a median survival, from salvage HFSRT, of 11 months, without clinically significant acute morbidity and only one case of late grade 3 CNS toxicity (78). However, no direct comparison between salvage SRS and HFSRT is available. Defining target volumes for SRS and HFSRT is controversial and variable. A variety of dose-fractionation regimens, target volumes, and stereotactic systems have been used in the treatment of rGBM. These approaches have not been subjected to randomized comparison, so the optimum technique is yet to be established.

CONVENTIONALLY FRACTIONATED RADIATION

Despite most studies discussing re-irradiation with SRS or HFSRT focus, cfRT may theoretically allow more generous target volumes. A large retrospective series of 172 recurrent glioma patients included 59 patients with GBM, who attained a median survival of 8 months, with only one patient developing radiation necrosis (91). The median dose was 36 Gy (15–62 Gy; 2 Gy/day) and was delivered to the enhancing volume plus a 0.5–1 cm margin. There are not enough clinical data available to recommend cfRT for routine use in the recurrent setting. Practitioners using large-volume re-irradiation should take into account brain tolerance data to reduce the risk of radionecrosis (51).

BRACHYTHERAPY

Brachytherapy has also been evaluated for use in rGBM. Typically performed after resection of recurrent disease, brachytherapy features a sharp dose gradient. Strategies include permanent iodine 125 (I-125) seeds and a silicone balloon catheter system containing I-125 solution. Retrospective studies on I-125 have demonstrated median survivals, from the time of brachytherapy, ranging from 11 to 15 months (92). A review by Combs et al. reported high reoperation rates and radionecrosis incidence (93). It should be noted that patients that are selected for brachytherapy are normally those with resectable tumors, good PS, and small volume of disease. As given in the literature on SRS, selection bias confuses interpretation. Also, the patients receiving brachytherapy need to be healthy enough to undergo surgery and, generally, have localized rather than diffuse recurrences.

COMBINATION TREATMENT

Several studies have addressed the combination of chemotherapy with re-irradiation. A few studies have explored TMZ, given its efficacy at radiosensitization in the upfront treatment of GBM. TMZ plus re-irradiation has been found to be safe and effective. Other studies have explored the addition of bevacizumab, which may block hypoxia factor-mediated angiogenesis, which is upregulated by RT (94–96). Moreover, bevacizumab has been used to treat radionecrosis and may reduce its risk following re-irradiation (97–99). A few small studies have investigated concurrent TMZ and SRS or FSRT. Median OS ranged between 8 and 9.7 months. Regarding toxicity, it was mild in one study, while neurologic toxicity was reported

in two other studies (8–13%) (89, 100, 101). Several studies have investigated adding bevacizumab to SRS (72, 88, 102–105). A prospective trial at Memorial-Sloan Kettering Cancer Center, investigating the safety of SRS (30 Gy in 5 fractions) with bevacizumab, reported no radionecrosis among 25 recurrent malignant glioma patients, but three patients discontinued treatment because of bevacizumab grade 3 related toxicity. They documented a 50% RR in the GBM population and a median OS of 12.5 months (102, 106). Another prospective study, in 15 patients with recurrent malignant gliomas, reported one grade 3 and no grade 4–5 toxicities, while QoL and neurocognition were well maintained (88). Median OS from SRS was 14.4 months. A retrospective study from Duke University, in 63 recurrent malignant glioma patients, found that median survival was longer for those who received bevacizumab around the time of SRS, than those who did not (11 vs. 4 months for GBM patients, $P = 0.014$) (72). Several studies have reported relatively low rates of adverse radiation events in patients treated with bevacizumab and SRS/HFSRT (72). Minniti et al. combined HFSRT (25 Gy in five fractions) with bevacizumab or fotemustine and described significantly better OS and PFS in the bevacizumab cohort (107). These studies are nonrandomized, so selection bias remains a serious concern and additional data are required.

SECOND-LINE CHEMOTHERAPY

Several chemotherapy options are available for second-line treatment, but no standard of care has been established. Comparing results between the various studies, particularly the older ones, is difficult, given the heterogeneity of inclusion criteria, patient characteristics, and choice of endpoints and response criteria. Many trials included patients with anaplastic gliomas (WHO grade 3) and GBM (WHO grade 4). Trials conducted prior to the establishment of standard first-line TMZ chemoradiotherapy often included patients not pretreated with TMZ. In addition, most studies were noncomparative, or did not include an adequate control arm. Most considered the PFS6 and the median OS since recurrence as the primary end points. Although PFS6 is considered a reliable measure of tumor control and a strong predictor of survival, this is influenced by other rescue therapies (108). Regarding radiological response assessments, they were often incompletely reported, with most using the Macdonald criteria. The following sections will describe the most relevant trials performed to date with respect to the medical treatment of rGBM.

NITROSOUREA MONOTHERAPY AND COMBINATION REGIMENS

Nitrosoureas are DNA alkylating agents, namely carmustine (BCNU), lomustine (CCNU), nimustine (ACNU), and fotemustine. They are characterized by high lipophilicity and thus can cross the blood–brain barrier, making them useful in the treatment of brain tumors such as GBM (109). Table 2 summarizes nitrosourea-based trials in rGBM. Nitrosoureas, particularly BCNU, were the chemotherapeutic agents of choice for first-line treatment of GBM in the 1970s and 1980s. Based on two phase II trials, TMZ was approved for recurrent high-grade gliomas, and nitrosoureas were relocated into second-line therapy (126, 127).

TABLE 2
Retrospective studies and clinical trials with nitrosourea in recurrent GBM (nitrosourea + bevacizumab combination studies are described in Table 4)

Reference	Arm 1	Arm 2	Arm 3	Previous TMZ	Relapse	n	Phase	RR (%) Arm 1 vs. 2 vs. 3	PFS (months) Arm 1 vs. 2 vs. 3	PFS6 (%) Arm 1 vs. 2 vs. 3	OS (months) Arm 1 vs. 2 vs. 3	
Single-arm monotherapy trials												
(110)	BCNU	–	–	No	1st	40	II	15	–	17.5	7.5	
(111)	FOT	–	–	Yes	1st	27	II	30	5.7	48.2	9.1	
(112)	FOT	–	–	Yes	1st	43	II	7	1.7	20.9	6.0	
(113)	FOT	–	–	Yes	1st	50	II	18	6.1	52	8.1	
(114)	FOT	–	–	Yes	1st	40	II	25	6.1	61	11.1	
Single-arm combination therapy trials												
(115)	BCNU + IRI	–	–	Yes	1st	42	II	21.4	3.9	30.3	11.7	
(116)	BCNU + TMZ	–	–	No	NA	38	II	5.6	2.5	21	7.8	
(117)	FOT + TMZ	–	–	Yes	NA	20	Prospect.	NA	4.3	40	NA	
Randomized trials												
(118)	BCNU or TMZ	ERL	–	Some (number of pts NA)	1st	106	II	10 vs. 4	2.4 vs. 1.8	24.1 vs. 11.4	7.3 vs. 7.7	
(119)	CCNU	Enzastaurin	–	NA	1st, 2nd	265	III (2:1)	4 vs. 3	1.6 vs. 1.5	19 vs. 11	7.1 vs. 6.6	
(120)	CCNU + P	CED	CCNU + CED	Yes	1st	325	III (1:2:2)	8 vs. 14 vs. 16	2.7 vs. 3.1 vs. 4.2	24.5 vs. 16 vs. 34.5	9.8 vs. 8.0 vs. 9.4	
(121)	CCNU + Galun	Galun	CCNU + P	NA	NA	158	II (2:1:1)	1 vs. 5 vs. 0	1.8 vs. 1.8 vs. 1.9	–	6.7 vs. 8.0 vs. 7.5	

TABLE 2

Retrospective studies and clinical trials with nitrosourea in recurrent GBM (nitrosourea + bevacizumab combination studies are described in Table 4) (Continued)

Reference	Arm 1	Arm 2	Arm 3	Previous TMZ	Relapse	n	Phase	RR (%) Arm 1 vs. 2 vs. 3	PFS (months) Arm 1 vs. 2 vs. 3	PFS6 (%) Arm 1 vs. 2 vs. 3	OS (months) Arm 1 vs. 2 vs. 3
Retrospective studies											
(122)	PCV	-	-	4 pts	NA	63	Retrospect.	17.5	NA	29	7.7
(123)	PCV	-	-	12 pts	1st	86	Retrospect.	3.5	4.0	38.4	7.8
(124)	ACNU ± combination ^a	-	-	Yes	≥1st	32	Retrospect.	6.3	2.7	20	6.7
(125)	BCNU	-	-	24 pts	1st, 2nd, 4th	35	Retrospect.	6.2	2.6	13	5.1

ACNU, nimustine; BCNU, carmustine; CCNU, lomustine; CED, cediranib; ERL, erlotinib; FOT, fotemustine; Galun, galunisertib; IRI, irinotecan; NA, not available; OS, median overall survival; P, placebo; PCV, procarbazine-lomustine-vincristine; PFS, median progression-free survival; PFS6, 6-month PFS; Pts, patients; Retrospect., retrospective; RR, response rate; TMZ, temozolomide.

^aCombination with teniposide (n = 17) or cytarabine (n = 1).

Two phase II trials and a retrospective study assessed the efficacy of BCNU monotherapy regimens in rGBM (110, 118, 125). They reported a PFS6 and a median OS of 13.0–17.5% and 5.1–7.5 months, respectively. RRs were limited and no complete remission was observed. The predominant side effects were hematologic and long-lasting hepatic and pulmonary toxicity. Although BCNU regimens have shown similar efficacy to other cytotoxic therapies, toxicity can be substantial, and the patient recovers slowly, such that the administration of other drugs in the case of further tumor progression can be infeasible (110). BCNU was also evaluated in combination with other agents, such as irinotecan and TMZ, in two phase II studies, with a median OS of 7.8–11.7 months (115, 116). These data demonstrate that BCNU is an effective agent in the treatment of rGBM, but at present its use in clinical practice is limited.

In a small retrospective study, with 32 patients pretreated with TMZ, ACNU was given alone ($n = 14$) or in combination with teniposide ($n = 17$) or cytarabine ($n = 1$), yielding a PFS6 of 20% and a median OS of 6.7 months (124). Hematological toxicity was substantial (grade 3 or 4 in 50% of patients). Three phase II–III randomized trials compared lomustine as monotherapy with investigational agents, namely enzastaurin, cediranib, or galunisertib (119–121). In all three trials, the results were comparable between arms, pointing toward relevant activity of the control arm or lack of efficacy of the investigational agent. PFS6 ranged from 11 to 34.5%, median OS from 6.6 to 9.8 months, and observed RRs were low (0–16%). Four prospective phase II trials, using different schedules of administration, evaluated fotemustine in TMZ pretreated patients at first recurrence/relapse of GBM (111–114). These four studies, encompassing 160 patients, showed a PFS6 of 20.9–61% and a median OS of 6 to 11 months. The best efficacy and toxicity profile was obtained with a low-dose induction regimen (fotemustine 80 mg/m² on days 1, 15, 30, 45, and 60, followed by a 4-week rest period) ensued by a maintenance therapy (80 mg/m² every 4 weeks) in nonprogressive patients (114). However, these data were derived from phase II trials with a small sample of patients. Phase III studies are required to determine the efficacy and safety of fotemustine, in the treatment of rGBM, after TMZ. The efficacy of PCV (procarbazine–lomustine–vincristine) was described in two retrospective studies (122, 123). They included 149 patients, of whom 16 received previous TMZ treatment. Similar results were described, with PFS6 of 29–38.4% and a median OS of 7.7–7.8 months. As expected, grade 3/4 hematologic toxicity was the most common (26%); pulmonary fibrosis was not reported (123). There is also suggestion that MGMT promoter methylation may be predictive of responsiveness to this class of agents (7, 128). In summary, different nitrosoureas show comparable efficacy in monotherapy, remaining an option in the treatment of rGBM. However, their toxicity profile, particularly hematological, limits the combination with other agents, as well as a more widespread use.

TEMOZOLOMIDE MONOTHERAPY AND COMBINATION REGIMENS

In both trials leading to the approval of TMZ, the sdTMZ schedule was used (126, 127). Four other prospective single-arm trials, all without previous TMZ treatment, used the same schedule and reached similar results with a PFS6 rate of 21–32% and a median OS of 7.0–9.9 months (129–132). Table 3 reviews

TABLE 3
Retrospective studies and clinical trials with temozolomide in recurrent GBM (temozolomide + nitrosourea combination studies are described in Table 2)

Reference	Arm 1	Arm 2	Arm 3	Previous TMZ	Relapse	n	Phase	RR (%) Arm 1 vs. 2 vs. 3	PFS (months) Arm 1 vs. 2 vs. 3	PFS6 (%) Arm 1 vs. 2 vs. 3	OS (months) Arm 1 vs. 2 vs. 3
Single-arm monotherapy trials											
(126)	TMZ 5/28	–	–	No	1st	126	II	8	2.1	18	5.4
(129)	TMZ 5/28	–	–	No	2nd	22	II	23	NA	32	7.6
(130)	TMZ 5/28	–	–	No	2nd	42	II	19	NA	24	7.0
(133)	TMZ 42/70	–	–	No	NA	28	II	0	2.3	19	7.7
(134)	TMZ 7/14	–	–	No	1st, 2nd, 3rd	21	II	10	4.9	48	NA
(131)	TMZ 5/28	–	–	No	1st	13	Prospect.	NA	NA	21	NA
(135)	TMZ 21/28	–	–	No	1st	33	II	9	3.7	30	9.2
(136)	TMZ cont.	–	–	Yes	NA	12	Prospect.	17	6	58.3	11
(132)	TMZ 5/28	–	–	No	NA	19	Prospect.	24	2.2	22	9.9
(137)	TMZ 7/14	–	–	9 pts	NA	64	II	NA	5.5	43.8	NA
(138)	TMZ q12h for 28 days	–	–	No	≥1st	68	II	31	4.2	35	8.8
(139)	TMZ 21/28	–	–	Yes	NA	27	II	7	NA	0	5.1 ^a

Table continued on following page

TABLE 3 Retrospective studies and clinical trials with temozolomide in recurrent GBM (temozolomide + nitrosourea combination studies are described in Table 2) (Continued)

Reference	Arm 1	Arm 2	Arm 3	Previous TMZ	Relapse	n	Phase	RR (%) Arm 1 vs. 2 vs. 3	PFS (months) Arm 1 vs. 2 vs. 3	PFS6 (%) Arm 1 vs. 2 vs. 3	OS (months) Arm 1 vs. 2 vs. 3
RESCUE study (140)	TMZ cont.	—	—	Yes	1st	91	II	NA	NA (all), 3.6 (early), 1.8 (extended), 3.7 (rechallenge)	23.9 (all), 27.3 (early), 7.4 (extended), 35.7 (rechallenge)	9.3 (all)
(141)	TMZ cont.	—	—	Yes	1st	38	II	5	3.9	32.5	9.4
(142)	TMZ 21/28	—	—	Yes	1st	47	II	12.8	2.3	23	13
(143)	TMZ 7/14	—	—	Yes	1st	27	II	11.1	4.2	33.3	6.9
(144)	TMZ 21/28	—	—	Yes	1st	58	II	13	1.8	11	11.7
(145)	TMZ 7/14	—	—	Yes	≥1st	40	II	NA	1.8	10	5
Single-arm combination therapy trials											
(146)	TMZ + CIS	—	—	No	NA	20	II	10	4.9	35	NA
(147)	TMZ + CIS	—	—	No	1st	50	II	20.4	4.2	34	11.2
(148)	TMZ + Lipo. DOX	—	—	No	1st	22	II	18	3.6	32	8.2
(149)	TMZ + IRI	—	—	No	NA	91	I	12	2.6	27.3	NA
(150)	TMZ + O ⁶ -BG	—	—	Yes	NA	34	II	3	1.7	9	4.5
(151)	TMZ + INF- α	TMZ + PEG-INF- α 2b	—	No	NA	63	II ^b	12 vs. 3	3.6 vs. 4.4	31 vs. 38	7.2 vs. 10

TABLE 3 Retrospective studies and clinical trials with temozolomide in recurrent GBM (temozolomide + nitrosourea combination studies are described in Table 2) (Continued)

Reference	Arm 1	Arm 2	Arm 3	Previous TMZ	Relapse	n	Phase	RR (%) Arm 1 vs. 2 vs. 3	PFS (months) Arm 1 vs. 2 vs. 3	PFS6 (%) Arm 1 vs. 2 vs. 3	OS (months) Arm 1 vs. 2 vs. 3
(152)	TMZ + BVZ	-	-	NA	2nd, 3rd	15	I-II	NA	2.4	6.7	3.6
(153)	TMZ + Sorafenib	-	-	Yes	1st to 6th	32	II	3	1.5	9.4	9.6
(154)	TMZ + BVZ	-	-	Yes	1st, 2nd, 3rd	32	II	28	3.7	18.8	8.6
(155)	TMZ + BVZ	-	-	Yes	1st	32	II	40.6	4.2	21.9	7.3
(156)	TMZ + ABT- 414	-	-	NA	NA	18	I	22.2	NA	NA	NA
Randomized trials											
(127)	TMZ	PCZ	-	No	1st	225	II	5 vs. 5	2.8 vs. 1.9	21 vs. 8	NA
(157)	TMZ 5/28	TMZ 21/28	PCV	No	1st	330 ^c	II	NA	5.0 vs. 4.2 vs. 3.6 ^c	NA	8.5 vs. 6.6 vs. 6.7 ^c
(158)	TMZ + BVZ	BVZ + ETOP	-	Yes	NA	23	II	0 vs. 0	1.0 vs. 1.9	0 vs. 7.7	2.9 vs. 4.4
(159)	TMZ 21/28	Afatimb	TMZ 21/28 + Afatimb	Yes	1st	119	II	19 vs. 2.4 vs. 5	1.9 vs. 1 vs. 1.5	2.3 vs. 3 vs. 10	10.6 vs. 9.8 vs. 8
DIRECTOR trial (160)	TMZ 7/14	TMZ 21/28	-	Yes	1st	105	II	8 vs. 16	NA	17.1 vs. 25	9.8 vs. 10.6

Table continued on following page

TABLE 3 Retrospective studies and clinical trials with temozolomide in recurrent GBM (temozolomide + nitrosourea combination studies are described in Table 2) (Continued)

Reference	Arm 1	Arm 2	Arm 3	Previous TMZ	Relapse	n	Phase	RR (%) Arm 1 vs. 2 vs. 3	PFS (months) Arm 1 vs. 2 vs. 3	PFS6 (%) Arm 1 vs. 2 vs. 3	OS (months) Arm 1 vs. 2 vs. 3
Retrospective studies											
(161)	TMZ	–	–	Yes	1st, 2nd	9	Retrospect.	44.4	7.0	NA	12
(162)	TMZ + resection + MITOX	TMZ + resection	TMZ	No	1st	276	Retrospect.	NA	70.7 vs. 64 vs. 39.3	NA	11 vs. 8 vs. 5
(163)	TMZ (PD during TMZ)	TMZ (SD during TMZ)	–	Yes	1st	47	Retrospect.	0.0 vs. 17.2	NA	26.3 vs. 28.6	6.6 vs. 5.3
(164)	TMZ + CEL	–	–	24 pts	1st, 2nd	28	Retrospect.	10.7	4.2	43	16.8

ACNU, nimustine; BCNU, carmustine; CCNU, lomustine; CED, cediranib; CIS, cisplatin; cont., continuous; DOX, doxorubicin; ERL, erlotinib; FOT, fotemustine; Galun, galunisertib; IFN, interferon; IRI, irinotecan; Lipo, liposomal; MITOX, mitoxantrone; NA, not available; O⁶-BG, O⁶-benzylguanine; OS, median overall survival; P, placebo; PCV, procarbazine-lomustine-vincristine; PCZ, procarbazine; PD, progression disease; PFS, median progression-free survival; PFS6, 6-month PFS; Pts, patients; Retrospect., retrospective; RR, response rate; SD, stable disease; TMZ, temozolomide.

^aOS from all patients; 27 patients with glioblastoma, 15 with anaplastic astrocytoma, and 5 with miscellaneous brain tumors; OS of glioblastoma patients was not reported separately.

^bTwo single-arm phase II studies: one with short-acting (IFN) and another with long-acting (pegylated) interferon $\alpha 2b$.

^cTwo hundred and seventy seven patients with glioblastoma, 53 with anaplastic astrocytoma, and 20 with miscellaneous brain tumors; data of glioblastoma patients was not reported separately.

TMZ-based trials in rGBM. Different schedules of TMZ were experimented to increase dose intensity, aimed at overcoming TMZ resistance by cumulative depletion of MGMT (165). The main alternative schedules were continuous low dose (40–50 mg/m² daily), 3 weeks on/1 week off (75–100 mg/m² for 21 days every 28 days), 1 week on/1 week off (150 mg/m² for 7 days every 14 days), but other dose-dense schedules are described (133–145). The toxicity profile did not vary between the different schemes. Besides the fact that the studies did not have a comparator arm, the heterogeneity in the inclusion criteria, regarding the number of recurrences and previous treatments, limits the comparison of efficacy data. The RESCUE phase II trial examined the best timing for TMZ rechallenge, by prospectively dividing the 91 GBM patients into three groups, according to the “TMZ-free interval”: early group (progression during the first six cycles of adjuvant TMZ); extended group (progression while receiving extended adjuvant TMZ, beyond the standard six cycles, but before completion of adjuvant treatment); and rechallenge group (progression after completion of adjuvant treatment and a treatment-free interval greater than 2 months). The “early” and “rechallenge” groups, respectively, showed comparable PFS6 rates of 27.3% and 35.7%, with median PFS of 3.6 and 3.7 months, experiencing most benefit than the “extended group” (PFS6 of 7.4%, median PFS of 1.8 months). The authors considered the possibility that the PFS6 results in the “early” group could be attributable to pseudoprogression (140).

Four randomized phase II clinical trials were conducted using single-agent TMZ (127, 159, 166, 167). A randomized trial comparing sdTMZ with procarbazine, in TMZ-naïve patients, revealed a PFS6 of 21% versus 8%, with a median OS 1.5 months longer in the TMZ arm (127). Brada et al. compared two different TMZ schedules with PCV, before TMZ became first-line standard, in patients with recurrent high-grade glioma (no separate data for GBM patients were provided) (166). In this trial, TMZ (both arms combined) did not display a clear benefit compared with PCV. It also showed that TMZ dose-intense regimens do not provide a survival or PFS benefit compared with standard doses, in the treatment of TMZ-naïve patients. The DIRECTOR trial compared two dose-dense regimens of TMZ (120 mg/m²/day, 1 week on/1 week off versus 80 mg/m²/day, 3 weeks on/1 week off), in patients with GBM at first progression, after TMZ chemoradiotherapy and at least two maintenance TMZ cycles (160). The outcome was comparable between arms regarding efficacy, safety, and tolerability. The most important result of this trial was the strong prognostic role of the MGMT promoter methylation status in patients rechallenged with TMZ. PFS6 was increased by 5.8-fold (39.7 % in patients with methylated MGMT versus 6.9 % in unmethylated tumours), and OS at 12 months by 2.4-fold. Also, a significantly improved outcome was demonstrated in patients with an interval above 2 months from previous TMZ, and largely confined to patients with MGMT methylated promoter (160). Wick et al. conducted a retrospective review of 80 patients with recurrent glioma (45 with GBM) rechallenged with various TMZ schedules (163). Upon progression, those who had stable disease and a TMZ-free interval of at least 8 weeks were treated with the same or an alternative regimen of TMZ; the group progressing under TMZ received an alternative regimen. The efficacy results were comparable between groups and no clear evidence of cumulative toxicity has emerged (163). Considering the small numbers of patients in most studies and the wide range of TMZ regimens tested, there was no evidence that one

metronomic schedule was superior over the other in terms of efficacy or safety. Numerous other studies evaluated TMZ-based combination regimens in rGBM but have failed to deliver conclusive efficacy beyond single-agent activity of TMZ. Those combination partners prospectively evaluated in single-arm designs were bevacizumab, interferon- α 2b, sorafenib, O6-benzylguanine, irinotecan, cisplatin, liposomal doxorubicine, and ABT-414 (146–156, 158).

BEVACIZUMAB MONOTHERAPY AND COMBINATION REGIMENS

The first documented use of bevacizumab in GBM was a small series of patients with rGBM treated by Stark-Vance et al. (Table 4) (168). The authors used the combination of bevacizumab with irinotecan, which showed activity, with acceptable toxicity profile. Several prospective phase II studies were subsequently conducted. Two phase II studies, by Vredenborg et al., using the same combination, achieved a RR of 57–60.9%, PFS6 rate of 30–46%, and a median OS of 9 to 10 months (171, 172). Previous reports on salvage therapy for rGBM showed inferior efficacy results, with RR of 5–10%, PFS6 rate of 9–25%, and median OS of 5 to 6 months (108, 202, 203). In 2009, FDA approved bevacizumab for patients with rGBM, based on the results of two phase II prospective studies (64, 65). However, in Europe, bevacizumab was not approved because of lack of a bevacizumab-free control arm. The BRAIN study, a phase II noncomparative trial, randomized patients to bevacizumab plus irinotecan or bevacizumab monotherapy (64). RR was 37.8 and 28.2% for the combination and monotherapy arms, respectively, and PFS6 was similar between the groups (50.3 and 42.6%), which compared favorably with historical controls. Numerous other retrospective studies addressing the combination of bevacizumab plus irinotecan described similar results (191–193, 196, 199, 201). Several phase II trials evaluated the combination of irinotecan with bevacizumab, and two trials added a third combination partner, cetuximab or carboplatin (171–173, 176, 178, 179). RR ranged from 25 to 60.9%, PFS6 between 28 and 46.5%, and median OS between 6.7 and 9.7 months. A retrospective analysis by Nghiemphu et al. compared two groups: one with bevacizumab in combination with different chemotherapy agents, and the other, a control group, without bevacizumab. The authors found a significant improvement in PFS ($P = 0.01$) and OS ($P = 0.04$) in favor of the group treated with bevacizumab (195).

Numerous studies have assessed bevacizumab in combination with other agents, namely etoposide, TMZ, fotemustine, dasatinib, temsirolimus, erlotinib, sorafenib, panobinostat, or vorinostat (154, 158, 175, 177, 179–181, 183, 184, 187–189). In randomized trials involving two arms—one with bevacizumab in combination with experimental agents (irinotecan, carboplatin, vorinostat, or dasatinib) and the other with bevacizumab alone—it was found that both arms showed comparable efficacy, leading to the conclusion of poor efficacy of the experimental agent, without valid evidence regarding the single-agent activity of bevacizumab. A recent Dutch, open-label, three-group multicenter phase II trial (BELOB) reported promising results with bevacizumab combined with lomustine (128). Improved OS at 9 months (59% vs. 43% vs. 38%) and PFS6 (41% vs. 13% vs. 16%) were seen in the combination arm compared with single-agent lomustine and single-agent bevacizumab, respectively. Effectively, this was the first trial

TABLE 4 Retrospective studies and clinical trials with bevacizumab in recurrent GBM

Reference	Arm 1	Arm 2	Arm 3	Relapse	n	Phase	RR (%)		PFS (months)		OS (months)	
							Arm 1 vs. 2	vs. 3	Arm 1 vs. 2	vs. 3	Arm 1 vs. 2	vs. 3
Single-arm monotherapy trials												
(65)	BVZ	-	-	1st	48	II	35		3.7	29	7.2	
(169)	BVZ	-	-	≥1st	50	II	24.5		-	25	6.5	
(170)	BVZ	-	-	1st	29	II	27.6		3.3	33.9	10.5	
Single-arm combination therapy trials												
(171)	BVZ + IRI	-	-	NA	35	II	57.0		5.5	46.0	9.7	
(172)	BVZ + IRI	-	-	NA	23	II	60.9		4.6	30	9.2	
(173)	BVZ + IRI	-	-	NA	57	II	37		-	-	-	
(174)	BVZ + IRI	-	-	1st to 6th	37	Prospect.	63.9		5.0	44.3	9.0	
(175)	BVZ + ETOP	-	-	1st, 2nd, 3rd	27	II	23		-	44.4	10.7	
(176)	BVZ + IRI + CETUX	-	-	1st	32	II	26		-	33	6.7	
(177)	BVZ + Erlotinib	-	-	1st, 2nd, 3rd	25	II	50		-	29.2	10.5	
(178)	BVZ + IRI	-	-	NA	32	II	25		5.2	28	7.9	
(179)	BVZ + IRI + CARBO	-	-	1st, 2nd, 3rd	40	II	33		-	46.5	8.3	
(154)	BVZ + TMZ	-	-	1st, 2nd, 3rd	32	II	28		3.7	18.8	8.6	

Table continued on following page

TABLE 4 Retrospective studies and clinical trials with bevacizumab in recurrent GBM (Continued)

Reference	Arm 1	Arm 2	Arm 3	Relapse	n	Phase	RR (%)		PFS (months)		PFS6 (%)		OS (months)	
							Arm 1 vs. 2	vs. 3	Arm 1 vs. 2	vs. 3	Arm 1 vs. 2	vs. 3	Arm 1 vs. 2	vs. 3
(180)	BVZ + Tem	-	-	NA	13	II	0		1.8		-		3.5	
(181)	BVZ + Sora	-	-	NA	54	II	18.5		2.9		20.4		5.6	
(182)	BVZ + FOT	-	-	1st	54	II	52		5.2		42.6		9.1	
(183)	BVZ + Pano	-	-	1st, 2nd	24	II	29.2		5.0		30.4		9.0	
(184)	BVZ + VOR	-	-	NA	40	II	22.5		-		30		10.4	
Randomized trials														
(64)	BVZ	BVZ + IRI	-	1st, 2nd	167	II	28.2 vs. 37.8		4.2 vs 5.6		42.6 vs. 50.3		9.2 vs. 8.7	
(152)	BVZ + TMZ	-	-	2nd, 3rd	15	I-II	NA		2.4		6.7		3.6	
(158)	BVZ + TMZ	BVZ + ETOP	-	NA	23	II	0 vs. 0		-		0 vs. 7.7		2.9 vs. 4.4	
BELOB trial (128)	BVZ	CCNU	BVZ + CCNU 110/90	1st	148	II	38 vs. 5 vs. 63/34		3.0 vs. 1.0 vs. 11.0/4.0		16 vs. 13 vs. 50/41		8 vs. 8 vs. 16/11	
(185)	BVZ	BVZ + CCNU	-	1st, 2nd, 3rd	68	II	-		4.1 vs. 4.3		-		Pts with 1st relapse: 8.8 vs. 13.1	
(186)	BVZ	BVZ + CARBO	-	1st	110	II	6 vs. 14		3.5 vs. 3.5		18 vs. 15		7.5 vs. 6.9	
(187)	BVZ	BVZ + VOR	-	1st	90	II	-		3.6 vs. 4.2		-		7.0 vs. 8.3	
(188)	BVZ + P	BVZ + Dasa	-	NA	121	II (1:2)	26.5 vs. 18.3		-		18.4 vs. 27.2		7.9 vs. 7.2	
(155)	BVZ + TMZ	-	-	1st	32	II	40.6		4.2		21.9		7.3	
(189)	BVZ + CCNU	CCNU	-	1st	437	III (2:1)	-		4.2 vs. 1.5		-		9.1 vs. 8.6	

TABLE 4
Retrospective studies and clinical trials with bevacizumab in recurrent GBM
 (Continued)

Reference	Arm 1	Arm 2	Arm 3	Relapse	n	Phase	RR (%)		PFS (months)		PFS6 (%)		OS (months)	
							Arm 1 vs. 2	vs. 3	Arm 1 vs. 2	vs. 3	Arm 1 vs. 2	vs. 3	Arm 1 vs. 2	vs. 3
Retrospective studies														
(168)	BVZ + IRI	-	-	NA	21	Retrosp.	42.9 ^b	-	-	-	-	-	-	-
(190)	BVZ + IRI or CARBO or ETOP	-	-	1st to 6th	14	Retrosp.	40 ^a	-	-	-	-	-	-	-
(191)	BVZ + IRI	-	-	1st to 5th	13	Retrosp.	77	-	-	-	-	-	6.3	-
(192)	BVZ + IRI	-	-	1st to 10th	27	Retrosp.	-	3.8	17	7.1	7.0 ^b	-	-	-
(193)	BVZ + IRI	-	-	≥1st	20	Retrosp.	47.4 ^b	4.2 ^b	25 ^b	42 ^a	-	-	-	-
(194)	BVZ + IRI or CARBO or CCNU or ETOP	-	-	1st to 7th	55	Retrosp.	34.1 ^b	-	-	-	-	-	-	-
(195)	BVZ + IRI or CARBO or CCNU or ETOP	Control group (various drugs with no BVZ)	-	1st to 3rd	20	Retrosp.	-	4.3 vs. 1.8 ^a	41 vs. 18 ^a	9.0 vs. 6.1 ^a	-	-	-	-
(196)	BVZ + IRI	-	-	≥1st	51	Retrosp.	67.6	7.6	63.7	11.5	-	-	-	-

Table continued on following page

TABLE 4
Retrospective studies and clinical trials with bevacizumab in recurrent GBM
 (Continued)

Reference	Arm 1	Arm 2	Arm 3	Relapse	n	Phase	RR (%)		PFS (months)		OS (months)
							Arm 1 vs. 2	vs. 3	Arm 1 vs. 2	vs. 3	
(171)	BVZ + CARBO or IRI or BCNU or CCNU or Erlotinib or ETOP	–	–	2nd (after BVZ)	54	Retrosp.	0 ^a	–	–	2 ^b	–
(172)	BVZ + CARBO + ETOP	–	–	1st to 5th	6	Retrosp.	83	–	–	22	7.0
(197)	BVZ	–	–	1st, 2nd	50	Retrosp.	42	–	–	42	8.5
(198)	BVZ	BVZ + IRI or CARBO or TMZ	–	2nd, 3rd	24	Retrosp.	50 vs. 19 ^a	–	–	0 vs. 14 ^a	1.5 vs. 5.2 ^a
(199)	BVZ + IRI	–	–	1st to 5th	93	Retrosp.	56	5.1	–	42	8.8
(200)	BVZ ± IRI or CARBO	–	–	2nd, 3rd	14	Retrosp.	29 ^a	4.0 ^a	–	29 ^a	7.8 ^a
(201)	BVZ + IRI	PCV	–	1st	60	Retrosp.	66.0 vs 11.0	5.0 vs. 3.0	–	–	9.0 vs. 5.0

BCNU, carmustine; BVZ, bevacizumab; CARBO, carboplatin; CETUX, cetuximab; CCNU, lomustine; Dasa, Dasatinib; EVE, everolimus; ETOP, etoposide; FOI, fotemustine; IRI, irinotecan; NA, not available; OS, median overall survival; P, placebo; Pano, Panobinostat; PCV, procarbazine-lomustine-vincristine; PFS, median progression-free survival; PFS6, 6-month PFS; Pts, patients; Retrosp., retrospective; RR, response rate; Sora, Sorafenib; Tem, temsirolimus; TMZ, temozolomide; VOR, vorinostat.

^aFor overall group. ^bIncludes patients with GBM and other high-grade gliomas.

with bevacizumab in rGBM to demonstrate an improvement in a primary OS endpoint, suggesting increased effectiveness with the combination of bevacizumab and lomustine versus each of these agents alone. Therefore, a randomized phase III trial was performed, comparing bevacizumab–lomustine with single-agent lomustine (189). Unfortunately, a benefit in OS was not observed, while the improvement in PFS for the combination arm was maintained. A crossover to bevacizumab occurred in 35.5% of patients, which may account for these results. To evaluate the efficacy of bevacizumab beyond the second-line treatment, Piccioni et al. performed a retrospective analysis of 468 GBM patients treated at different recurrences (first, second, third, or more), including 80 who were treated upfront. The authors found that PFS and OS were similar for all three recurrence groups (median 4.1 and 9.8 months, respectively) (204). These data suggest that bevacizumab could have a role in the treatment of GBM independent of the line of therapy, and that a deferred use of bevacizumab seems not to decrease effectiveness. When comparing the results of available phase II trials on bevacizumab, alone or in combination with irinotecan, with those of standard cytotoxic chemotherapy, in rGBM, several findings are clear: bevacizumab alone has activity and increases RR, PFS6, and median PFS; on the other hand, the impact on OS is less clear.

Tumor-Treating Electric Fields for Glioblastoma

CONCEPT

Tumor-Treating Fields (TTFields) has been called the “fourth cancer treatment modality,” after surgery, RT, and pharmacotherapy. It’s a locoregionally antimetabolic treatment that delivers low-intensity, intermediate-frequency (200 kHz), alternating electric fields, through four transducer arrays, consisting of nine insulated electrodes applied to the shaved scalp and connected to a portable device (11). *In vitro* studies have shown that TTFields arrests cell division and kills tumor cells through multiple mechanisms, namely, misalignment of microtubule subunits during division, aberrant chromosomal segregation, and cytoplasmic blebbing during anaphase.

CLINICAL TRIALS

Clinical effectiveness and feasibility of TTFields was first tested in 10 patients with rGBM, with PFS6 and median survival doubling that of historic controls (205).

Two pivotal randomized trials studied TTFields in rGBM (EF-11) and nGBM (EF-14).

In EF-11 trial, a total of 237 rGBM patients, after initial treatment with RT-TMZ, were randomized 1:1 to either the novel TTFields therapy (120 patients) or to treatment according to investigator’s choice (117 patients). Although EF-11 did not meet its primary endpoint of improving OS, similar median OS, and PFS in both arms, it established TTFields as noninferior to chemotherapy (206). In addition, the favorable QoL and toxicity profile led to FDA approval, in 2011, of TTFields as a therapeutic option for use in rGBM. The EF-14 trial, an open-label phase 3 study, enrolled 695 patients and evaluated the efficacy and safety of

TTFields in combination with TMZ maintenance treatment, after chemoradiation therapy for patients with nGBM. The trial was terminated based on the results of the preplanned interim analysis that evaluated the outcomes of the first 315 patients and showed a significant improvement in PFS and OS. The percentage of patients alive at 2 years was 43% in the TTFields/TMZ group and 29% in the TMZ alone group ($P = 0.006$) (207). In October 2015, the FDA approved TTFields for use in nGBM patients. National Comprehensive Cancer Network has further incorporated TTFields in their updated guidelines (208).

ISSUES

TTFields are particularly safe, since no additional systemic toxicity was observed with the addition of this technology. The most common side effects are mild to moderate skin reactions beneath the transducer arrays, observed in 44% of patients, and grade 3 skin reactions in 1–2 % of patients. Additional research is warranted, in order to identify which patients are most likely to be responsive to TTFields. Benefit was present across all subgroups studied (according to age, PS, MGMT methylation status, and EOR), but the follow-up remains short, and some subsets are rather small in number. Detailed subgroup analyses are to be performed on the final and validated dataset. Although approximately three-quarters of patients, in EF-14, had a treatment compliance of 75%, this is an important issue unique to this therapy, since it requires >18 h of usage per day. Another important point is the high cost of this therapeutic approach (about \$20,000 monthly). Strong price regulation by health authorities could make this technology more affordable and consequently accessible to patients (209). TTFields plus TMZ represents the first major advance in the field of GBM therapy in roughly a decade, and it should be considered for patients with nGBM and no contraindications.

Although showing significant improvements in survival, the results still underscore that the majority of patients did not survive beyond 2 years, highlighting the need for additional improvements in GBM therapeutic strategies. Due to its unique and localized mechanism of action, and general absence of systemic toxicity, TTFields is particularly well suited for combination therapies, such as immunotherapy and targeted therapies (210).

Glioblastoma in the Elderly

GBM is diagnosed at a median age of 64 years, and the incidence peaks between 75 and 84 years (15.24/100,000) (211). With aging population, this incidence is expected to increase. The poor survival rates associated with GBM (about 5% at 5 years) get even poorer in patients over 65 years (less than 2.1% at 5 years) (212). Age has long been recognized as the most important prognostic factor. Elderly patients tend to have more comorbidities and worse PS than their younger counterparts diagnosed with GBM. Similarly, their tumors seldom have favorable molecular features (IDH mutations occur in less than 2% of the tumors) (213). As a result, these patients have frequently been undertreated and underrepresented in clinical trials.

SURGERY

Several retrospective studies have shown an increase in OS, in elderly patients submitted to surgical resection (as opposed to biopsy) (206, 214–216). In the study by Keime-Guibert, and in the NOA-08 and the Nordic trials, the EOR was identified as an independent prognostic factor. As such, age alone should not preclude an attempt at complete resection (8, 206, 217).

RADIOTHERAPY

RT was associated with a statistically significant, although modest, gain in OS, when compared to best supportive care (BSC), in patients aged over 70 years (206). The study was interrupted after the first interim analysis due to superiority of RT. There was no difference between the two groups, regarding QoL and NCF. Roa et al. compared hypofractionated RT (HFRT; 40 Gy in 15 fractions over 3 weeks) with cfRT (60 Gy in 30 fractions over 6 weeks) in 100 patients aged 60 years or older (218). There was no difference in OS between the two groups and the patients treated with HFRT required less increment in post-therapy corticosteroid dose (23% vs. 49%; $P = 0.02$). Although the study could not show that the two treatments were equivalent, together these results led to the adoption of HFRT as a valid option in the treatment of elderly patients, particularly those with a poor PS.

CHEMOTHERAPY

In an ANOCEF phase II trial, 70 patients aged 70 years or older, with a KPS under 70%, received sdTMZ until disease progression (219). The 25 weeks median OS compared favorably with the 12–16 weeks expected with BSC alone. Furthermore, there was an improvement in functional status in 33% of patients. Patients with MGMT promoter methylation had longer PFS and OS. A previous study by Chinot and colleagues had shown similar survival results (220).

CHEMOTHERAPY AND RADIOTHERAPY

The 5-year analysis of the hallmark study by Stupp et al. (3) showed a survival benefit for the combination in all subgroups, including patients aged over 60 years, RPA class V, and unmethylated MGMT promoter (211). However, an analysis by age strata showed a diminishing benefit of TMZ association with increasing age, especially in patients older than 65 years (221). Caution should be made in interpreting these results as the group over the age of 65 years represented only 15% of the study population. The 2014 EANO guidelines reflected this concern by including the multimodality treatment as an option for fit elderly patients (9). A retrospective analysis of 293 patients over the age of 65 showed a benefit for the combined regimen (222). A retrospective survey of the National Cancer Database yielded similar results, with combined modality treatment showing superiority over both chemotherapy alone and RT alone, in a group of 16,717 patients, with nGBM, aged 65 years or older (223). Two prospective randomized studies addressed the question of which single modality treatment would be best for

elderly patients. In the Nordic trial, patients over the age of 60, with ECOG PS 0-3, were randomized between three treatment arms: sdTMZ (up to six cycles), HFRT (34.0 Gy administered in 3.4 Gy fractions over 2 weeks), and cfRT (217). Fewer patients completed the course of RT in the standard group (72%) compared to the hypofractionated one (95%), which may partly account for the poor results obtained in the former group. TMZ and HFRT yielded similar survival results and, particularly in patients over the age of 70, these were significantly better than the ones for cfRT. MGMT promoter methylation was predictive of response to TMZ. In the NOA-08 trial, patients older than 65 years, with a KPS >50%, were randomized to receive TMZ (100 mg/m², given on days 1–7 of 1 week on, 1 week off cycles) or cfRT (8). The trial showed noninferiority of TMZ and there were no differences regarding QoL either, between the treatment arms. MGMT promoter methylation was both prognostic and predictive of response to TMZ. Event-free survival was longer in patients with methylated MGMT promoter treated with TMZ than in those submitted to RT (8.4 vs. 4.6 months) and the opposite was true for the group of patients with an unmethylated promoter (3.3 vs. 4.6 months). Taken together, these results support the role of MGMT promoter methylation in the choice of single modality treatment, in elderly patients with nGBM.

The EORTC 26062-22061 trial was designed to assess whether the addition of TMZ to HFRT would translate into a survival benefit (224). A total of 562 patients, aged 65 years or older, were randomized, with the combined modality being associated with a longer median OS (9.3 vs. 7.6 months; $P < 0.001$) and PFS. Again, MGMT promoter methylation was predictive of response to TMZ (median OS: 13.5 months with RT-TMZ vs. 7.7 months with RT alone; $P < 0.001$). Although not reaching statistical significance, the combined therapy also offered a survival advantage to the group with an unmethylated MGMT status (median OS: 10.0 months vs. 7.9 months; $P = 0.055$). QoL was similar in both study groups. An unsolved question is which RT-TMZ scheme is better for fit elderly patients. Some retrospective studies have addressed this issue. Arvold and colleagues found no differences in OS, between cfRT-TMZ and HFRT-TMZ, after adjusting for selection bias (225). Minitti also found no differences in OS and PFS between the two groups (226). However, cfRT-TMZ was associated with more neurologic toxicity ($P = 0.01$), lowering of KPS scores over time ($P = 0.01$), and higher post-treatment dosing of corticosteroid ($P = 0.02$). There are numerous issues that make this a special and challenging group. The definition of elderly varies widely between studies limiting the extrapolation of results to our patients' population. Several trials lack NCF and QoL evaluations necessary for us to understand the real impact of the current available therapies in the elderly patient. The assessment of MGMT promoter methylation, although proven useful in this population, is not readily available to all. Furthermore, these patients are frequently only submitted to biopsy, which may render insufficient samples to MGMT promoter status determination.

Elderly patients with GBM have a worse prognosis than their younger counterparts. This relates to several factors, namely, poorer PS, comorbidities, delay in diagnosis (symptoms are often interpreted as signs of depression or dementia), and IDH wild-type tumors. These patients tend to be undertreated solely based on their biological age and because, they are underrepresented in clinical trials, there's a paucity of data guiding clinical decisions. Based on prospective trials, HFRT has

become standard in this population and proven equivalent to TMZ, and MGMT promoter methylation status has a paramount importance in the choice of single modality therapy. In addition, there's now evidence that the addition of TMZ to HFRT yields an increase in OS, representing an alternative to the Stupp regimen, in elderly patients with a good PS.

Supportive Care

The patient with GBM is, simultaneously, a patient with cancer and one with a progressive neurological disease. As such, there are certain specificities regarding not only the most frequent symptoms exhibited but also some end-of-life (EOL) care issues. Patients with primary brain tumors were found to have poorer PS, higher levels of nursing and social support, and more family overburden than other palliative care patients. Disorientation and confusion were also more frequent. Conversely, general EOL symptoms, such as dyspnoea, nausea, vomiting, anorexia, constipation, and pain, were experienced less frequently (227). Palliative care should aim at improving QoL, both for the patient and the caregiver, and is not limited to the EOL stage. The timing of its introduction, in the management of GBM patients, is an understudied issue. The experience with metastatic nonsmall cell lung cancer indicates improvements in QoL, mood, and symptom burden, as well as better EOL care and even extended survival, with early initiation of palliative care (228). Disease itself, along with GBM treatment side effects and symptomatic medication (namely antiepileptic drugs), affects cognition and impairs decision-making, very often early in the disease course (229, 230). As such, timely involvement of the patient in treatment decisions (including supportive measures ahead) is of paramount importance. Two systematic reviews of studies addressing the EOL phase, in high-grade gliomas, showed a high burden of symptoms, namely reduced consciousness (44–90%), dysphagia (10–85%), headache (36–62%), seizures (10–56%), focal neurological deficits (>50%), cognitive disturbances (>30%), confusion (15–51%), and poor communication (64–90%) (227, 231–236).

SEIZURES

Approximately 30% of glioma patients have a seizure during the last week of life, regardless of having or not having a history of seizures (235, 237). As mentioned earlier, prophylactic use of anticonvulsant drugs is not indicated in patients without history of seizures (12). Enzyme inducers antiepileptic drugs should be avoided as they interact with commonly used cytotoxic agents and dexamethasone, having the potential to reduce their efficacy (238). Valproic acid is an enzyme inhibitor that may increase therapeutic levels of antineoplastic agents. Several reports also suggest a direct antitumor effect, but this is yet to be proven (239). Levetiracetam is the most studied of the recent anticonvulsants in this setting. It appears safe without major interactions with the commonly used drugs (240). At the EOL, dysphagia and altered consciousness are common and impair the administration of oral medication. As a result, half of the patients taper antiepileptic drugs in the last week of life, with one-third experiencing seizures (237).

As the occurrence of seizures is associated with nonpeaceful death, it is important to maintain antiepileptic treatment throughout the EOL phase (231). This can be achieved by using alternative routes of administration. For patients in home care, rectal diazepam and buccal or intranasal midazolam are convenient alternatives (241).

DEPRESSION

Diagnosis can be difficult as all the symptoms of a major depressive disorder, with the exception of suicidal thoughts, can be attributed to the tumor, its treatment, or both (242). Selective serotonin reuptake inhibitors may be considered as first-line treatment of depression, as they have not shown increased toxicity in glioma patients and they are not associated with increased incidence of seizures in the general population (242, 243). The benefit and feasibility of psychotherapy in treating depression and anxiety in glioma patients is uncertain (242).

RAISED INTRACRANIAL PRESSURE

Raised intracranial pressure, as a result of tumor growth and cerebral edema, can cause headache, nausea, vomiting, somnolence, and visual disturbances. Corticosteroids are the treatment of choice. Dexamethasone is often used for its long half-life, anti-inflammatory activity, and absence of mineralocorticoid effect (244). Corticosteroids must be tapered as soon as possible and kept in the lowest dose capable of controlling symptoms. Attention must be given to the complications associated with prolonged steroid use.

CONFUSION

Confusion is a major cause of distress for the patient and his caregivers. It can arise from the tumor itself, or be caused by pain, infection, metabolic imbalances, symptomatic treatments, fecaloma, bladder retention, intracranial hemorrhage, or seizures (244). Neuroleptics, such as haloperidol, risperidone, and olanzapine, are often needed. Opioids and sedatives are also options if pain or sleep and behavioral disorders coexist.

ISSUES AT EOL CARE

During the EOL phase, dysphagia and altered consciousness will impair nutrition and hydration, and the administration of symptomatic medication, namely, corticosteroids and anticonvulsants. As mentioned before, these last ones should be kept, but steroids are often tapered and discontinued in the last days of life, when the patient is already unconscious, to avoid futile prolongation of life. Maintenance or withdrawal of artificial nutrition and hydration and symptomatic medications are EOL decisions common to all glioma patients. Another topic that can be discussed with the patient in advance is palliative sedation. Between 13 and 45% of patients were reported to have received it. Refractory seizures, agitation, and delirium are among the reasons that lead to its institution (245). The knowledge on palliative care in glioma patients is largely based on retrospective studies and

on extrapolations from studies performed on other cancer patients. Properly conducted prospective and interventional investigations, specifically designed for glioma patients, addressing the specificities of this population are needed.

Conclusion

Despite maximal safe surgical resection and combined chemotherapy and RT, GBM retains a poor prognostic value. To date, excluding TTFields, no new agents improve survival when added to standard therapy. Although MGMT promoter methylation is predictive of response to TMZ, its role in the choice of first-line therapy is currently limited to the elderly GMB patients. No standard of care is established in the recurrent setting. Bevacizumab clearly impacts PFS, although its role in OS is less certain. TMZ rechallenge is a treatment option, especially for MGMT promoter-methylated rGBM. All in all, while efforts are being put in strategies to prolong OS, enhancing QoL for these patients must be a priority.

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