Current Medical Treatment of Glioblastoma

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Abstract Glioblastoma is the most common adult malignant primary brain tumor. Despite the advances in therapeutic options, survival of patients with glioblastoma remains dismal at 15–18 months. Current standard of care for newly diagnosed glioblastoma is maximal possible safe resection consistent with the preservation of neurologic function followed by concurrent temozolomide with radiation and adjuvant. Treatment options at recurrence include surgical resection with or without the placement of carmustine wafers, re-irradiation and chemotherapeutics such as nitrosoureas (lomustine, carmustine) or bevacizumab, a monoclonal antibody targeting vascular endothelial growth factor (VEGF).

Keywords Glioblastoma · Chemotherapy · Clinical trials · Angiogenesis · Targeted therapy

Contents

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1 Introduction

Medical therapies are an important component of treatment of glioblastoma. Adjuvant treatment of glioblastoma consists of temozolomide and radiation therapy. A number of cytotoxic and targeted agents are used in the therapy of recurrent glioblastoma. This review will focus on the role of the cytotoxic and targeted therapies in the management of glioblastoma.

2 Newly Diagnosed Glioblastoma

2.1 Cytotoxic Chemotherapy

A landmark international phase III trial established the role of temozolomide in the treatment of newly diagnosed GBM [1]. This trial randomized 573 patients with newly diagnosed GBM to receive either radiotherapy alone or radiotherapy and concomitant temozolomide followed by six cycles of adjuvant temozolomide. In the control group, patients received fractionated focal radiotherapy at 2 Gy per fraction 5 days per week, over 6 weeks, for a total dose of 60 Gy. In the experimental arm, patients received radiotherapy with concomitant temozolomide (75 mg/m^2 daily for 6 weeks). Patients then received up to six cycles of adjuvant temozolomide (150–200 mg/m^2 days 1–5, every 28 days). Two hundred and eighty six patients received radiotherapy alone while 287 received both radiotherapy and temozolomide. The median survival with radiotherapy plus temozolomide was 14.6 months compared to 12.1 months with radiotherapy alone. All patients in radiotherapy plus temozolomide group received prophylaxis for *Pneumocystis jiroveci* pneumonia with either inhaled pentamidine or oral sulfamethoxazole-trimethoprim during the concomitant phase. Grade 3–4 hematologic toxicity was noted in 7 % of patients during the concomitant phase and 14 % of patients in adjuvant phase. Fatigue was the most common nonhematologic adverse event. The 2-year survival in temozolomide plus radiotherapy group was 26 % whereas the radiotherapy alone group was 10 %. The survival advantage persisted at 5 years of follow up, 9.8 % in temozolomide group were alive at 5 years compared to 1.9 % in radiotherapy alone group [2].

A companion correlative study that evaluated tumor samples from 206 patients showed that methylation of the promoter region of the O^6-methylguanine DNA methyltransferase (MGMT) gene in the tumor was associated with superior survival [3]. O^6-methylguanine DNA methyltransferase removes the methyl group from the O6 position of guanine, reversing the cytotoxic effects of alkylating agents, making the tumor resistant to treatment. The methylation of the promoter region of MGMT results in inactivation of MGMT making the tumor more susceptible for damage by temozolomide therapy. Among MGMT-methylated patients, 5-year survival rate was 14 % in combined group compared to 5 % in radiotherapy alone group.

Recognizing that a different schedule of temozolomide may overcome chemotherapy resistance, alternative dosing schedules of temozolomide have been tried in the newly diagnosed glioblastoma [4]. A large phase III trial of 833 patients, RTOG 0525 was designed to test the efficacy of dose-dense temozolomide in newly diagnosed glioblastoma [5]. All patients received the standard concomitant phase of temozolomide and radiation for 6 weeks after initial surgical resection. In the adjuvant setting, the patients were randomized to standard adjuvant temozolomide or dose-dense temozolomide (75–100 mg/m^2 days 1–21, every 28 days). No statistically significant difference was seen in median PFS (5.5 months vs. 6.7 months) or OS (16.6 months vs. 14.9 months) in two arms. This trial confirmed the importance of MGMT methylation as a prognostic marker as it was associated with improved OS in both groups. There was increased grade 3/4 toxicity in dose-dense arm (53 %; $P < 0.001$), mostly lymphopenia and fatigue.

Strategies to increase the therapeutic ratio of temozolomide, such as the inhibition of DNA repair enzymes such as poly[ADP-ribose] polymerase [PARP] and base excision repair enzymes are being evaluated. These agents are being combined with radiation and chemotherapy to increase the cytotoxicity of the combination approach [6–8]. A cooperative group study of phase I/II study of iniparib, temozolomide, and radiotherapy in patients with newly diagnosed malignant glioma has completed accrual (NCT00687765). There is a planned Alliance study of veliparib and temozolomide following temozolomide and radiation in patients with newly diagnosed MGMT-methylated glioblastoma.

2.2 Carmustine Polymer (Gliadel) Wafers

The carmustine polymer wafer is a biodegradable matrix embedded with carmustine (bis-chloroethylnitrosourea) acting as extended release carrier system. Wafers are placed in the surgical cavity during tumor resection. They have been FDA approved for use in newly diagnosed and recurrent GBM during resection. They have not been compared directly with temozolomide in patients with newly diagnosed glioblastoma, and there are no data to support a clear survival advantage. A randomized trial compared carmustine polymer wafers to placebo in newly diagnosed high-grade gliomas [9]. Subgroup analysis showed median survival of 13.5 months in Gliadel wafers group compared to 11.4 months in placebo group in the 207 GBM patients; the difference was not statistically significant. Additional toxicities seen in the carmustine polymer group included cerebrospinal fluid (CSF) leak and intracranial hypertension (5 % vs. 1 % and 9 % vs. 2 % respectively) compared to placebo.

A recent observational study of 92 patients who underwent carmustine polymer wafers placement followed by concurrent chemoradiation with temozolomide reported a PFS and OS of 10.5 and 18.8 months, respectively [10]. Unclear if there is benefit of the addition of the carmustine wafer to standard chemoradiation.

2.3 Targeted Therapy

Angiogenesis is a highly regulated process necessary for new blood vessel formation and that occurs as a result of activation of a number of proangiogenic signaling pathways [11, 12]. Glioblastoma is one of the most vascularized tumors known, making antiangiogenic therapies a promising strategy [13, 14]. Glioblastoma is associated with a high degree of vascular proliferation [15, 16]. This results in upregulation of proangiogenic factors such vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), and platelet-derived growth factor (PDGF) [13]. Increased expression of VEGF in GBM correlates with increased tumor aggressiveness and poor survival [17]. Bevacizumab is a humanized monoclonal antibody that binds to the ligand VEGF-A, and the inhibition of the VEGF normalizes the vasculature of gliomas [18].

Two large randomized phase III trials (RTOG 0825 [19] and AVAglio [20]) examined the efficacy of bevacizumab in combination with radiation and temozolomide in patients with newly diagnosed GBM. In RTOG 0825, 637 patients were randomized to standard temozolomide and radiotherapy (control group-placebo) or bevacizumab in addition to standard temozolomide and radiotherapy (experimental group) [19]. Although PFS was increased in the bevacizumab arm (11 months vs. 7.3 months, $p = 0.004$), the improvement did not meet the prespecified criteria for a positive study. No difference was found between the two arms for OS (both 16 months). Patients with MGMT methylation had superior PFS and OS ($p < 0.001$). Neither the 9-gene signature nor MGMT predicted selective benefit for bevacizumab treatment, but best prognosis patients (MGMT methylation, favorable 9-gene) had a worse survival trend with bevacizumab (16 months vs. 25 months, $p = 0.08$). The study identified the PRO GBM panel as a gene signature that predicted for benefit with bevacizumab. However, this needs to be validated in prospective trial. Increased grade ≥3 toxicity was seen with bevacizumab group, mostly neutropenia, hypertension, and thrombo-embolic disease. Results of a quality of life analysis favored the chemoradiation alone group. Patients who underwent a biopsy were excluded from the trial due to the requirement of tissue for correlative studies, a group that may derive the most benefit with treatment with bevacizumab.

In the AVAglio study (Roche/Genentech sponsored), 921 patients were randomized to receive bevacizumab or placebo in combination with radiation and temozolomide. The addition of bevacizumab to radiation and temozolomide significantly prolonged PFS (HR 0.64, $p < 0.0001$; median 10.6 months vs. 6.2 months) as compared to radiation and temozolomide [20]. However, the addition of bevacizumab did not improve OS (16.8 months vs. 16.7 months, HR 0.88, $p = 0.1$). In this study, the patients treated on the experimental arm showed improved quality of life as measured by five scales of the QLQ-C30 and BN20 survey instruments. The patients treated on the experimental had longer time off from steroids and maintained their performance status longer as compared to the control group.

Patients with unmethylated MGMT glioblastoma have inferior outcomes as compared to those with MGMT-methylated glioblastoma and temozolomide is less

effective in these patients. Hence the GLARIUS trial eliminated the temozolomide in the experimental arm. In a phase II trial, 170 patients with unmethylated MGMT glioblastoma were randomized to bevacizumab with radiotherapy followed by maintenance bevacizumab and irinotecan (experimental arm) compared to standard temozolomide during radiation followed by 6 cycles of temozolomide (control arm) [21]. The progression-free survival at 6 months (primary endpoint) in experimental arm was superior (72 % vs. 26 %).

Cilengitide (EMD121974), an integrin inhibitor that showed some promise in recurrent glioblastoma [22, 23], was evaluated in newly diagnosed glioblastoma trials. In the CENTRIC study, 545 patients with newly diagnosed glioblastoma with MGMT promoter methylation were randomized to cilengitide in addition to standard radiation and temozolomide [24]. The overall survival was similar in both arms (26 months vs. 26 months), and the study did not show any additional benefit with cilengitide in this patient population [24]. The CORE trial, a three-arm multicenter phase II trial, randomized patients with unmethylated MGMT glioblastoma to standard (2 times a week) or intensive (5 times a week) cilengitide in addition to radiation and temozolomide compared to standard therapy of radiation and temozolomide (control group) [25]. There was suggestion of benefit of cilengitide with median OS of 16 months in the standard dose of cilengitide arm compared to the median OS was 13 months in the control group (HR 0.69; $p = 0.033$). However, this drug is not being further developed.

2.4 Summary and Recommendation

For newly diagnosed glioblastoma, we recommend participation in a clinical trial. In case the patient is not eligible for a clinical trial and has good performance status, we use 6 weeks of concurrent radiotherapy (60 Gy in 30 fractions) with daily temozolomide (75 mg/m^2) followed by adjuvant temozolomide (150–200 mg/m^2 day 1–5 every 28 days) for 6 cycles (level 1 evidence). It reasonable alternative to use up to 12 cycles however no trials have compared 12 versus 6 cycles; RTOG 0525 suggested a benefit for 12 months but the number were heavily weighted for patients who received 12 months of therapy so hard to interpret. For post-radiation temozolomide, dose-dense therapy did not show an advantage over the standard 5/28 day approach (Level 1 evidence). We prefer not to use adjuvant nitrosoureas or carmustine polymer wafers (often exclusion criteria for clinical trial participation).

3 Recurrent Glioblastoma

Treatment options for recurrent GBM must be tailored to the individual. Few agents have proven activity.

3.1 Cytotoxic Chemotherapy

For patients who recur after initial treatment with temozolomide and who are not candidates for a clinical trial and have with small tumors that are not very symptomatic, nitrosoureas or nitrosoureas containing regimen is a reasonable approach. Nitrosoureas such as lomustine, carmustine either as single agents or in combination —procarbazine, lomustine, and vincristine (PCV regimen) are commonly used in United States.

In a phase II study of 40 with recurrent glioblastoma patients treated with carmustine (BCNU) following surgery and standard radiotherapy, a median time to progression (TTP) of 13 weeks was noted [26]. Progression-free survival at 6 months was 17 %. Response to chemotherapy was a significant prognostic factor for TTP on multivariate analysis.

Two phase III trials of enzastaurin and cediranib used single-agent lomustine as the control arm [27, 28]. In the enzastaurin phase II trial, median PFS, PFS-6, and OS of 1.6, 19 %, and 7.1 months respectively were seen in the recurrent glioblastoma patients in the lomustine arm [27]. In the phase III trial that examined the efficacy of cediranib, the median PFS and OS with lomustine were 2.7 and 9.8 months, respectively [28]. Based on these data from these two large phase III trials, there has been renewed interest in using lomustine in the patients with recurrent glioblastoma who are not eligible for clinical trial or in whom bevacizumab is a not a preferred option.

A trial of 86 patients with recurrent glioblastoma evaluated procarbazine, lomustine, and vincristine (PCV) [29]. Median PFS of 17 weeks and PFS-6 of 38 % was seen and 3 patients achieved partial responses (PR). World Health Organization grade 3/4 hematologic toxicity of 26 % was the most common side effect noted on this study. Many investigators, however, do not use the PCV regimen in favor of single-agent lomustine due to the increased toxicity of the combination and the lack of blood–brain barrier penetration of vincristine.

Dose-dense or dose-intense or metronomic temozolomide has been evaluated in number of phase II studies of patients with recurrent malignant glioma [30–33]. In RESCUE study, a phase II study of recurrent malignant glioma, 120 patients were treated with continuous daily temozolomide, 50 mg/m^2/day [32]. 6-month progression-free survival (PFS-6) of 24 % was seen in the recurrent glioblastoma group.

3.2 Carmustine Polymer (Gliadel) Wafers

A phase III trial in the setting of recurrent high-grade gliomas enrolled 227 patients of which 145 had GBM [34]. The 6-month survival was 50 % greater in those implanted with Gliadel wafers as compared to placebo. Major adverse effects noted included seizures, cerebral edema, and intracranial infections. Given the heterogeneous patient population in this report, the role of carmustine wafers for any specific high-grade glioma histology is difficult to discern.

3.3 Targeted Therapies

The earliest report of bevacizumab use was from Dr. Stark-Vance, who treated 21 patients with recurrent high-grade glioma, including 11 patients with glioblastoma, with bevacizumab and irinotecan [35]. There were one complete response (CR), 8 PR, and 11 stable diseases (SD). The overall response rate (ORR) was 43 %.

The majority of initial clinical trials in high-grade gliomas utilized bevacizumab in combination with irinotecan based on the original combination regimen used in colorectal cancer. A phase II trial of 35 patients with recurrent glioblastoma evaluated bevacizumab and irinotecan [36]. The PFS-6 of 46 % and OS of 9.7 months led to a larger multicenter prospective randomized noncomparative trial, the BRAIN study [37]. In this study, 167 recurrent glioblastoma patients were randomized to treatment with bevacizumab with or without irinotecan. Overall response rates (ORR) of 38 % versus 28 %, PFS-6 of 50 % versus 46 %, and OS of 8.7 months versus 9.2 months were seen in the combination and bevacizumab alone arm, respectively. This trial showed improved PFS-6 and ORR compared to historical controls. Bevacizumab use was associated with a steroid sparing effect. In the NCI 06-C-0064E phase II trial, 48 patients with recurrent glioblastoma were treated with bevacizumab monotherapy, and received irinotecan at progression [38]. In this study, ORR of 35 % and PFS-6 of 29 % was noted, and there was no benefit of adding irinotecan at progression. Based on the ORR seen in the BRAIN trial and NCI 06-C-0064E trials, bevacizumab received the US FDA accelerated provisional approval in recurrent glioblastoma [37, 38]. However, the European regulatory authority did not approve bevacizumab for use in recurrent glioblastoma due to the lack of a control arm in these two trials.

Multiple chemotherapy or targeted agents have undergone extensive evaluation in combination with bevacizumab, primarily in recurrent glioblastoma. These include combination with etoposide [39], carboplatin [40], temozolomide [41] or alternative dosing [42] or lower dose [43]. The results of these studies have been comparable to the bevacizumab arm of the BRAIN study.

Two randomized phase II trials have evaluated the benefit of chemotherapy to bevacizumab. A phase II trial (CABARET) randomized patients to treatment with bevacizumab with or without carboplatin. The PFS-6 of 26 % and OS of 6.9 months for the combination were similar to PFS-6 of 24 % and OS of 6.4 months observed for bevacizumab monotherapy [28]. In the BELOB study, a Dutch three-arm multicenter randomized phase II study, 148 recurrent glioblastoma patients were randomized to bevacizumab, lomustine, or the combination of bevacizumab and lomustine. The PFS-6 was 16, 13, and 41 %, and the OS at 9 months was 38, 43, and 59 %, respectively [44]. The combination of bevacizumab and lomustine met the prespecified primary endpoint of OS at 9 months of 55 % and is undergoing evaluation in phase III study, EORTC (NCT01290939). Interestingly, the single-agent arm did far worse than other trials.

A number of agents targeting VEGF have been examined. Cediranib (AZD2171), an orally administered pan-VEGF receptor inhibitor, showed promising results in a

Table 1 Randomized trials in newly diagnosed glioblastoma with medical therapies (last decade)

Study (reference)	Number of patients	Treatment arms	PFS (months)	OS (months)	Comments
EORTC/NCI [1]	573	RT/TMZ versus RT	6.9 versus 5.0	15 versus 12	RT/TMZ superior to RT alone
RTOG 0525 [5]	833	Standard dose TMZ (days 1–5 every 28 days) versus dose-dense TMZ (days 1–21 every 28 days)	5.5 versus 6.7	17 versus 15	No significant improvement in OS or PFS with dose-dense TMZ/RT
RTOG 0825 [19]	637	RT/TMZ/Bev versus RT/TMZ	11 versus 7.3	16 versus 16	PFS longer in Bev group; no significant difference in OS
AVAGLIO [20]	921	RT/TMZ/Bev versus RT/TMZ	11 versus 6.2	17 versus 17	PFS longer in Bev group; no significant difference in OS
GLARIUS [21]	170	RT/TMZ/Bev + Bev/Iri[a] versus RT/TMZ	9.7 versus 6.0	17 versus 15	PFS-6 in Bev/Iri arm superior unmethylated MGMT GBM
CENTRIC [24]	545	RT/TMZ/CIL versus RT/TMZ	13 versus 11	26 versus 26	CIL did not prolong PFS or OS in methylated MGMT GBM
CORE [25]	265	RT/TMZ/CIL_2 versus RT/TMZ/CIL_5 versus RT/TMZ	5.6 versus 5.9 versus 4.1	16 versus 14 versus 13	Median OS increased with addition of CIL_2 but not with CIL_5 in unmethylated MGMT GBM

RT/TMZ-radiation with concurrent temozolomide followed by adjuvant temozolomide; *PFS* progression-free survival; *PFS* 6-progression-free survival at 6 months; *OS* overall survival; *RT* radiation therapy; *TMZ* temozolomide; *Bev* bevacizumab; *Iri* irinotecan; *MGMT* O^6 -methylguanine DNA methyltransferase; *CIL* cilengitide; CIL_2 cilengitide 2 times/week (standard dose); CIL_5 cilengitide 5 times/week (dose intense)

[a] Bev/Iri substituted for adjuvant temozolomide

Table 2 Randomized trials in recurrent glioblastoma with medical therapies (last decade)

Study (reference)	Number of patients	Treatment	PFS (months)	OS (months)	Comments
Bev versus Bev/Iri [35]	167	Bev versus Bev/Iri	46 % versus 50 %[a]	9.2 versus 8.7	No advantage to addition of irinotecan
Enzastaurin versus Lomustine [27]	266	Enzastaurin versus lomustine	1.5 versus 1.6	6.6 versus 7.1	PFS, OS not superior
REGAL [46]	325	Cediranib versus lomustine versus cediranib/lomustine	92 versus 82 versus 125 days	8.0 versus 9.8 versus 9.4	Cediranib-containing arms not superior to lomustine
CABARET [28]	122	Bev/Carboplatin versus Bev	26 % versus 24 %[a]	6.9 versus 6.4	Bev/Carboplatin not superior
BELOB [44]	140	Bev versus Lomustine versus Bev/Lomustine	3 versus 2 versus 4	38 % versus 43 % versus 59 %[b]	Bev/lomustine met primary endpoint of OS at 9 months (55 %). Phase III bev/lomustine versus lomustine ongoing

PFS progression-free survival; *OS* overall survival; *Bev* bevacizumab

[a] PFS_6 (PFS at 6 months)

single-center phase II study [45]. However, the phase III randomized trial did not show a statistical improvement in PFS with cediranib either as monotherapy or in combination with lomustine compared to lomustine alone in recurrent glioblastoma [46]. A phase II study of VEGF Trap (aflibercept), a recombinantly produced fusion protein that captures circulating VEGF and CT-322, showed minimal evidence of single-agent activity in recurrent malignant glioma [47]. Other antiangiogenic agents evaluated include enzastaurin, an inhibitor of protein kinase C-beta that targets VEGF as well as the mTOR pathway [27]. The phase III trial of enzastaurin compared to lomustine in recurrent glioblastoma concluded that enzastaurin did not have superior efficacy compared to lomustine [27].

Similarly trials targeting epidermal growth factor receptor (EGFR) using agents such as erlotinib and gefitinib have shown limited activity in recurrent glioblastoma [48–51]. Irreversible EGFR inhibitors such as afatinib did not show efficacy when used in alone or combination with temozolomide in recurrent GBM [52]. There is an ongoing phase II study with second-generation EGFR inhibitor, dacomitinib (NCT01112527). Other targeted agents including the mammalian target of rapamycin (mTOR) inhibitor, temsirolimus, and the farnesyl transferase inhibitor, tipifarnib, have shown minimal activity in recurrent glioblastoma [53–57].

3.3.1 Summary and Recommendation

For recurrent glioblastoma, we recommend participation in a clinical trial. In case the patient is not eligible for a clinical trial and has good performance status, we suggest systemic therapy often with a non-bevacizumab regimen such as lomustine. We use bevacizumab-based regimens for patients with symptoms related to a significant component of vasogenic edema or patients who have significant steroid requirements or intolerance. For patients who need bevacizumab and have not received lomustine, we prefer the combination of bevacizumab with lomustine (Level II evidence) (Tables 1 and 2).

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