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MINI REVIEW

An algorithm for chemotherapy treatment of recurrent glioma patients after temozolomide failure in the general oncology setting

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Abstract
Purpose The standard therapy for newly diagnosed malignant gliomas comprises surgery, radiotherapy, and commonly temozolomide chemotherapy. For recurrent or progressive disease after temozolomide failure, there is no consensus and only limited options for chemotherapy.
Methods We reviewed the English literature for phase II trials of therapies for recurrent malignant glioma conducted between January 2000 and September 2010. The search was supplemented by a review of articles published prior to 2000 on chemotherapy regimens that had shown activity on recurrent gliomas.
Results To guide practice in the general oncology setting, an algorithm was constructed according to the activity of the reported chemotherapies at the time of writing. Some molecular studies performed on tumor tissue may help guide the selection of chemotherapy. Methylated MGMT in tumor tissue correlates with increased sensitivity to alkylating agents such as fotemustine or other nitrosoureas. Depending on MGMT status and bone marrow reserve, treatment with fotemustine, bevacizumab, bevacizumab with irinotecan, or cis-retinoic acid (cRA), might be of value.
Conclusion Unfortunately, progress in the development of new and more effective chemotherapy agents has been very limited and leaves the clinician treating high-grade glioma patients at relapse with few good options. The suggested algorithm is our objective evaluation of the currently existing knowledge. Hopefully, the ongoing phase II and III trials will provide us the needed chemotherapy agents in the years to come.

Keywords Glioma · Glioblastoma · Chemotherapy · Temozolomide

Introduction

High-grade gliomas (WHO grade 3 and 4 gliomas), and especially glioblastoma, are among the most difficult cancers to treat with short survival and poor response to chemotherapeutic drug intervention [1]. The reasons for the poor efficacy of these agents include the blood–brain barrier, which forms a pharmacological sanctuary, the expression of multidrug resistance proteins in glioma tumor cells and associated capillaries [2], the genetic, molecular, and metabolic heterogeneity of glioma tumor cells [3], resistance mechanism to commonly used alkylating agents, and, possibly, defects of both humoral and cellular immunity [4]. Tumor stem cells that exist within malignant gliomas may provoke glioma development, perpetuation, and resistance to chemotherapy and radiation, accounting for the failure of conventional therapies and emergence of tumor recurrence [5]. In addition, radiation therapy, the primary treatment modality for gliomas, triggers several signal transduction pathways and toxic events to

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the tumor, such as direct DNA damage. This can lead either to cell death or to mutations in the surviving tumor cells that might result in subsequent emergence of resistant clones and recurrence [6].

In general, postoperative adjuvant radiation therapy and chemotherapy with second-generation monofunctional alkylating agent temozolomide (TMZ) became the standard care for newly diagnosed malignant gliomas soon after its introduction [7–9]. Unfortunately, high-grade gliomas usually recur despite treatment. In most cases, the radiographic determination of tumor growth is obvious, but sometimes radiation effect or outright radiation necrosis mimics tumor growth and requires different treatment. As a result, sometimes reoperation and/or biopsy is needed to confirm the diagnosis or to debulk tumor prior to chemotherapy. If surgery is not an option, specific imaging modalities, prior to initiation of secondary therapies, may help to establish the probability of tumor growth versus radiation effect [10–14].

For relapsed glioma patients who did not receive adjuvant TMZ chemotherapy, therapy with TMZ still remains a good choice [15, 16]. Some authorities recommend rechallenge with alternative dosing TMZ for recurrent malignant gliomas, even if patients had received previously standard TMZ chemotherapy [17–19]. Perry et al., using continuous dose-intense TMZ for recurrent or progressive gliomas on standard TMZ therapy, reported benefit with 6-month progression-free survival of 23.9% in patients with GBM and 35.7% in patients with anaplastic glioma [20]. In this review, we evaluated all major phase II trials for recurrent gliomas, published after the emergence of TMZ and all active chemotherapies prior to the TMZ era. Our goal was to construct an algorithm for the general oncologist, and not the specialist neuro-oncologist, on how to treat an individual patient with recurrent glioma after TMZ failure, depending on the individual patient characteristics.

Evaluation of phase II studies

The criteria used to evaluate the various therapies include response rate, which is associated with reduction in progression rate [21], histology, which is a dominant factor in determining outcome [22], and progression-free survival (PFS), which is a more reliable end point than overall survival since it reflects the true antitumor benefit of chemotherapy [23] (Table 1). In addition, a 6-month PFS is strongly associated with survival suggesting that it is a valid end point in recurrent glioma trials [24, 25]. Objective response as an end point in phase II glioma trials may have limitations, due to the frequent low response rates observed in recurrent glioma trials, rendering it extremely difficult to assess its predictive value to PFS and overall survival [26]. Furthermore, the radiologic assessment of response to treatment in patients with recurrent glioma is vulnerable to substantial inter-observer inconsistency [27]. However, if the treatment has efficacy and the objective response is substantial, it may be linked to survival and could be a reliable predictor of a treatment benefit in recurrent glioma patients [28].

Typically, the rate of 6-month progression-free survival (PFS-6) is 21% for TMZ-naïve patients with recurrent glioblastoma (GBM) after treatment with TMZ [15]. The PFS-6 in studies of patients with anaplastic glioma (AG) ranged from 37 to 41% [23]. After primary therapy with radiotherapy and TMZ followed by adjuvant TMZ, no standard salvage therapy exists for patients with high-grade glioma, although the FDA has approved recently an anti-angiogenic therapy with bevacizumab for recurrent GBM because of promising response rates and increased median PFS [29].

Molecular targeted therapies

What defines this therapeutic approach varies among physician scientists. On the one hand, alkylating agents that "target" DNA could be called targeted therapy, although most consider targeted therapy to be one that is directed toward specific signaling pathways, whether cell surface receptors, signaling proteins in the cytosol, or enzymes important to transcription or DNA effects in the nucleus. Unfortunately, many of the new purported targeted therapies are, in fact, drugs that target anywhere from three to more than five other proteins and thus are far from being specific and targeted therapies. Common among many of the reversible tyrosine kinase inhibitors is unexpected systemic toxicity based on their promiscuous behavior to receptor and intracellular kinases.

While many of the new targeted drugs have been studied alone, lack of definite activity in many cases has led to their use in combination with alkylating agents such as temozolomide or with other presumed targeting agents. Combination of molecularly targeted therapies, such as anti-angiogenesis through inhibition of the VEGFR pathway (e.g., bevacizumab), EGF receptor tyrosine kinase inhibitors (gefitinib and erlotinib), PDGF receptor inhibitors (imatinib), mTOR inhibitors (temsirolimus and everolimus), and protein kinase C-beta and other angiogenesis pathway inhibitors (vatalanib and enzastaurin) may be in theory more efficient therapies. However, the lack of specificity of many of the protein tyrosine kinase inhibitors has led to unexpected dose-limiting toxicities [30]. Unfortunately, most studies with such compounds, apart from few exceptions, have proven ineffective. For example, a phase II trial with a

Table 1 End points for evaluation of phase II clinical trials in recurrent glioma

Study	No. of patients	Age (range)	Karnofsky	Prior surgeries	Prior chemotherapy	Response	Survival	Comment
Hess et al. [21] Data from 8 consecutive phase II trials	375 total 225 GBM 150 AA	45 (15–82)	80 (60–100)	11% > 2	11% > 2	CR = 0.3% PR = 8.8% PD = 90.9%	52-week PFS = 48% (CR + PR) 52-week PFS = 28% (PD)	Response was associated with reduction in progression rate
Wong et al. [22] Data from 8 consecutive phase II trials	375 total 225 GBM 150 AA	45 (15–82)	80 (60–100)	11% > 2	11% > 2	CR + PR = 9.1%	Median PFS = 10 weeks (all) Median PFS = 9 weeks (GBM) Median PFS = 13 weeks (AA) Median OS = 30 weeks APF6 = 15% (GBM) APF6 = 31% (AA)	Histology was a dominant factor in determining outcome
Levin et al. [23] Data from 16 phase II trials	529 total	41 (36–47)	84 (80–88)		2.5% = 0 52% = 1 34% = 2 9% = ≥3	PR + CR = 10%	PFS6 = 15–41% PFS9 = 11–38% PFS12 = 9–33%	PFS is the reliable end point and not overall survival
Prados et al. [28] Analysis of data from BRAIN phase II trial	167 GBM BV:42.6% BV + CPT-11: 50.3%	54 (23–78) 57 (23–79)	70–100	1	100% = 1 (TMZ)	PR + CR = 32.9%	PFS6 = 42.6-50.3% Median PFS = 16.8 weeks (BV) Median PFS = 22.4 weeks (BV + CPT-11) Median OS = 36.8 weeks (BV) Median OS = 34.8 weeks (BV + CPT-11)	OR and PFS were significant predictors of survival
Ballman et al. [24] Pooled data from 16 phase II and phase III trials	345 GBM	54 (19–79)	ECOG status (0 to > 2)	1 (100%) 2 (72%)	1	ND	PFS6 = 9% OS12 = 14% Median PFS = 7.2 weeks Median OS = 20 weeks	PFS6 is a reasonable end point in phase II trials for recurrent GBM patients
Lamborn et al. [25] Pooled data from 12 published phase II trials	596 total 437 GBM 159 AG	49 (20–84)	60–100	1 (100%) 2 (15%)	23% = 0 51% = 1 23% = 2 3% = 3	PR + CR = 7%	AG-PFS (9 weeks) = 53% AG-PFS (18 weeks) = 33% AG-PFS (26 weeks) = 28% AG-Median PFS = 15 weeks AG-Median OS = 39 weeks GBM-PFS (9 weeks) = 44% GBM-PFS (18 weeks) = 25% GBM-PFS (26 weeks) = 16% GBM-Median PFS = 8 weeks GBM-Median OS = 30 weeks	PFS6 is a useful end point in phase II trials for recurrent glioma patients; status at earlier time points may be also useful, particularly in studies with negative results

APF6 progression-free at 6 months, *GBM* glioblastoma multiforme, *AA* anaplastic astrocytoma, *BV* bevacizumab, *PFS* progression-free survival, *OS* overall survival, *OS12* 12-month overall survival, *CR* complete response, *PR* partial response, *OR* objective response, *PD* progressive disease, *PFS6* progression-free survival at 6 months, *PFS9* progression-free survival at 9 months, *PFS12* progression-free survival at 12 months, *ND* not determined

combination of imatinib mesylate, an ATP-mimetic, tyrosine kinase inhibitor, plus hydroxyurea showed good tolerance, but only moderate activity in some patients with recurrent AG [31]. Similarly, administration of gefitinib (250 mg/d), an EGFR inhibitor, after first-line chemotherapy showed limited activity in patients with recurrent gliomas [32]. However, the maximum tolerated dose of gefitinib could be 500–1,000 mg/kg depending on the concomitant use of non-EIAEDs or EIAEDs, respectively [33]. Cetuximab, an EGFR antagonist, showed limited toxicity and activity against recurrent GBM independent of the EGFR status of the tumors [34]. Overall, studies on EGFR inhibitors found no significant activity of these agents in high-grade gliomas [35]. The phase II clinical trials for recurrent glioblastoma and anaplastic glioma after temozolomide failure are depicted in Tables 2 and 3, respectively.

Anti-angiogenesis

Recent research and therapy strategies have focused on understanding the mechanisms leading to the origin of tumor angiogenesis to develop new approaches that effectively block angiogenesis and promote tumor regression [36]. Angiogenesis can be targeted by molecules against the vascular endothelial growth factor (VEGF), or its receptor, VEGFR (small molecule tyrosine kinase inhibitors) [37]. Although antiangiogenic treatment is usually well tolerated, life-threatening complications can occur, such as thromboembolism, hemorrhage, and gastrointestinal perforation [38].

Bevacizumab is a humanized monoclonal antibody against VEGF-A, which has been shown to have significant biologic activity in patients with recurrent GBM [29] (Table 2). Bevacizumab seems to suppress the enhancing tumor recurrence more effectively than the non-enhancing infiltrative tumor [39]. It has been shown that while antiangiogenic therapy improves PFS, it may not prolong overall survival in patients with recurrent malignant glioma [40]. Other studies have demonstrated that bevacizumab improved survival, but it was unclear if it increased the invasiveness of the tumor [41]. Furthermore, patients who progressed on a regimen consisting of a combination of bevacizumab with chemotherapy rarely responded to a second bevacizumab-containing chemotherapeutic regimen [42].

Irinotecan (CPT-11)

Irinotecan, an inhibitor of topoisomerase I, crosses the blood–brain barrier and has antitumor activity against gliomas [43]. The activity of irinotecan may be limited, with the concomitant administration of enzyme-inducing antiepileptic drugs (EIAEDs), since the pharmacokinetic studies indicated that the total body clearance of irinotecan was markedly enhanced and the maximum tolerated dose was increased 3.5 times in this study population [44]. Cloughesy et al. reported in two studies with irinotecan (CPT-11) activity against recurrent glioma, especially with escalating doses, that patients on EIAEDs may be underdosed [45]. However, Prados et al. failed to show such an association, but the CPT-11 dose in patients who received EIAEDs was 750 mg/m^2, which was lower than the maximum of 1,700 mg/m^2 used in the previous study [46].

Thalidomide

Thalidomide, an antiangiogenic agent, has been considered a therapeutic option for patients with recurrent GBM after failure of other more active chemotherapeutic drugs, since it is generally well tolerated [47]. However, thalidomide as a single agent had very limited anti-tumor activity in patients with recurrent malignant gliomas [48].

Fotemustine

Fotemustine, a third-generation chloroethylnitrosourea given to recurrent glioma patients after TMZ failure showed very promising results and limited toxicity in three recent studies from Italy [49–51]. In addition, like other alkylating agents, fotemustine appears more effective in patients with O6-methylguanine-DNA methyltransferase (MGMT) gene promoter methylation [49].

Retinoids

Retinoic acid, a synthetic analog of vitamin A, has multiple biologic effects against malignant gliomas and may be suitable as a maintenance therapy for patients who enter remission after primary treatment [52]. An earlier study of cis-retinoic acid (cRA) in recurrent gliomas had indicated activity of this agent especially in GBMs [53]. A retrospective analysis of 82 patients with recurrent GBM, most of who had been previously heavily treated with chemotherapy, showed modest activity with cRA with response and stable disease of 45% and a median PFS of 19 weeks. However, in the subset of 11% who responded, the median PFS was 59 weeks [54]. Another synthetic retinoid derivative, fenretinide, has been inactive in a phase II trial of recurrent malignant glioma [55]. Similar results were obtained with all-trans-retinoic acid (tretinoin) [56].

Table 2 Results of phase II clinical trials in recurrent glioblastoma patients after temozolomide failure

Study	Treatment	No.	Toxicity levels 3/4	Response + stable disease, %	MPFS, weeks	PFS6 (95% CI)	Median OS, weeks	Comment
Franceschi et al. [32]	Gefitinib	16	None	17.9		12.5% (1.6–38.4%)	NC	Limited activity
Neyns et al. [34]	Cetuximab	55	13.6%	35.1	7.6	7.3% (0–14%)	20	Limited activity No differences between EGFR+ and EGFR−
Puduvalli et al. [64]	CPT-11 and thalidomide	32	56%	65.6	13	25% (14–46%)	36	CPT-11 with thalidomide is promising
Fadul et al. [65]	CPT-11 and thalidomide	16	37.5%	18.8		19% (4–46%)	41	Comparable to CPT-11 alone
De Groot et al. [74]	Carboplatin and erlotinib	43	100%	49.3	9	14% (4–24%)	30	Carboplatin with erlotinib has modest activity
Fabrini et al. [50]	Fotemustine	41	14%	62	23.6	48.7% (35.2–62.2)	NC	Fotemustine was safe and effective
Scoccianti et al. [51]	Fotemustine	27	14.8%	48.1	22.8	48.1% (39.1–57.1)	36.4	Fotemustine was safe and effective
Prados et al. [46]	CPT-11	38	On EIAED = 0 (Not on EIAED) = 19.6%	NC		15.7% (7–31%).		Ineffective
Reardon et al. [70]	CPT-11 and celecoxib	33	On EIAED = 0 (Not on EIAED) = 21.6%	55.8	11.1	27.5% (15.5–48.6%)	31.1	CPT-11 and celecoxib had some activity
Bokstein et al. [63]	CPT-11 plus bevacizumab	17	10%	55	17	25% (NC)	28	Bevacizumab and irinotecan in low doses was active with minimal toxicity
Vredenburgh et al. [58]	CPT-11 plus bevacizumab	35	1 CNS bleed 31% stopped treatment due to toxicity	57	24	46% (32–66%)	42	Active treatment
Vredenburgh et al. [60]	CPT-11 plus bevacizumab	23	2 toxicity-related deaths	95.6	20	30% (16–57%)	40	Active regimen
Friedman et al. [59]	CPT-11 plus bevacizumab or bevacizumab only	82 85	65.8% 46.4%	37.8* 28.2*	22.4 16.8	50.3% (36.8–63.9%) 42.6% (29.6–55.5%)	35 37	Bevacizumab and irinotecan or bevacizumab alone are active

Table 2 continued

Study	Treatment	No.	Toxicity levels 3/4	Response + stable disease, %	MPFS, weeks	PFS6(95% CI)	Median OS, weeks	Comment
Kreisl et al. [29]	Bevacizumab followed by bevacizumab plus CPT-11	48	31% 12.5% removed from study due to toxicity	71	16	29% (18–48%)	31	Single-agent bevacizumab had activity
See et al. [54]	cRA	82	16.5% 1 death	46	10	19% (12–30%)	24.6	Modest efficacy
Walbert et al. [78]	6-thioguanine followed by lomustine or temozolomide and capecitabine plus celecoxib	43	18% grade 3 and 6% grade 4 myelotoxicity	45	7	14% (7–29%)	32	Similar to other lomustine studies

Patients had one to seven previous chemotherapies, including temozolomide; *MPFS* median progression-free survival, *OS* overall survival, measured from time of relapse to death, *PFS6* progression-free survival at 6 months, *EIAEDs* enzyme-inducing antiepileptic drugs, *EGFR* epidermal growth factor receptor, *EGFR+* amplified EGFR, *EGFR−* normal EGFR, *cRA* 13-cis-retinoic acid, *NC* not clear

* Objective response

Combination chemotherapy

Bevacizumab and irinotecan

A combination of bevacizumab at 10–15 mg/kg every 3 weeks with irinotecan at 125–340 mg/m^2 depended on the use or not of EIAEDs and, when administered at various schedules, showed significant activity in anaplastic glioma patients with PFS6 of 55% and median OS of 65 weeks [57]. Activity of this regimen with acceptable toxicity was also documented in multiple phase II trials of only GBM patients [58, 59] or studies that combined a mixture of recurrent GBM and AG patients [60–63].

Other irinotecan-based combinations

Puduvalli et al. reported that a combination of CPT-11 with the anti-angiogenesis agent thalidomide resulted in potentially promising results in 32 previously treated GBM patients, 83.8% of whom had temozolomide-based chemotherapies. The PFS6 in this study was 14% and the median overall survival was 30 weeks. However, in that study there were four deaths, two of which were possibly due to treatment-related toxicity [64]. A smaller study in 16 patients with recurrent GBM using the same agents failed to show any additional benefit from the addition of thalidomide to irinotecan [65]. A combination of CPT-11 with VM-26, a topoisomerase II inhibitor, showed no synergy between the two drugs and the results were comparable to those when each drug was used individually [66].

In a phase I study, the combination of BCNU with escalating dose of weekly administered CPT-11 was evaluated. From this study, it was determined that the recommended CPT-11 dose for patients on EIAEDs was 125 mg/m^2, and for patients not on EIAEDs it was 225 mg/m^2 [67]. However, a phase II trial employing such a combination resulted in comparable results to that of CPT-11 alone and increased toxicity [68]. Similarly, ACNU, another nitrosourea given alone or in combination with teniposide or cytarabine in patients with GBM after TMZ failure resulted in limited activity and considerable toxicity [69]. The combination of CPT-11 and celecoxib, a selective COX-2 inhibitor, was well tolerated and had a marginal activity against heavily pretreated recurrent glioma (mostly GBM) patients with PFS6 of 25.1% [70].

Other chemotherapeutic combinations

Addition of metronomic etoposide in bevacizumab-treated patients with recurrent glioma had no additional benefit compared to bevacizumab alone, but resulted in increased toxicity [71]. A combination of carboplatin and high-dose

Table 3 Phase II clinical trials in recurrent anaplastic glioma patients after temozolomide failure

Study	Treatment	No	Toxicity levels 3/4	Response + stable disease, %	MPFS, weeks	PFS6, %	PFS12, %	Median OS, weeks	Comment
Desjardins et al. [31]	Imatinib mesylate plus hydroxyurea	32	23%	43	11	24	14	33	Anti-tumor activity in some AG patients
Chamberlain and Glantz [86]	CPT-11	22 (AO)	14%	59	18	33	4.5	22	Modest activity in recurrent 1p19q co-deleted AO
Fabrini et al. [50]	Fotemustine	9	14%		37	66	NR	NC	Fotemustine was safe and effective
Fabi et al. [49]	Fotemustine	26	35%	54	NC	NC	NC	NC	Fotemustine was effective, especially with MGMT promoter methylation
Prados et al. [46]	CPT-11	13	Grade 4 (EIAED) = 0	ND	ND	23.1	ND	ND	Ineffective
Desjardins et al. [57]	CPT-11 plus bevacizumab	33	1 CNS bleed 1 TTP	94	30	55	39	65	Active regimen
Taillibert et al. [87]	CPT-11 plus bevacizumab	25 (AO)	24% intratumoral bleed symptomatic bleed 4%	88	20	42	ND	NR	Effective therapy for recurrent AO No relation to 1p19q co-deletion
Vredenburgh et al. [58]	CPT-11 plus bevacizumab	9	NC	100	30	56	ND	NR	Active regimen with acceptable toxicity
Chamberlain and Johnston [88]	Bevacizumab	22 (AO)	41%	73	27	68	23	34	Efficacy and acceptable toxicity
Walbert et al. [78]	6-Thioguanine followed by lomustine or temozolomide and capecitabine plus celecoxib	23 of 31 on the lomustine arm	18% grade 3 and 6% grade 4 myelotoxicity	68	24	44	44	54	Effective with acceptable toxicity

Patients had one to six previous chemotherapies, including temozolomide; anaplastic glioma (AG) included patients with anaplastic astrocytoma, anaplastic oligodendroglioma and anaplastic mixed glioma; *AO* anaplastic oligodendroglioma, *MPFS* median progression-free survival, *OS* overall survival, measured from time of relapse to death, *PFS6* progression-free survival at 6 months, *PFS12* progression-free survival at 12 months, *EIAEDs* enzyme-inducing antiepileptic drugs, *TTP* thrombotic thrombocytopenic purpura, *MGMT* O6-methylguanine-DNA methyltransferase, *NC* not clear, *ND* not determined, *NR* not reached

tamoxifen in a mixture of patients with recurrent malignant gliomas of various histologies showed a median OS of 56 weeks similar to other active regimens and equivalent to those found using tamoxifen as monotherapy [72]. The use of pegylated liposomal doxorubicin to improve better penetration through the blood–brain barrier, alone or in combination with high-dose tamoxifen, resulted in PFS6 of 15%, and median TTP of 17 weeks, suggesting moderate effectiveness in patients with recurrent high-grade glioma [73]. A combination of carboplatin at a dose of AUC 6 mg ml/min administered every 28 days, and erlotinib 150 mg/day had modest activity with median PFS of 9 weeks, PFS6 of 14%, and median OS of 30 weeks [74].

Nitrosourea combinations have long been popular and efficacious, although considerably more toxic than temozolomide-based treatments. Lomustine alone [75] or in combination with other agents [76] has demonstrated activity against recurrent GBM after temozolomide failure. Prior to temozolomide, a chemotherapy combination was developed called TPCH (6-thioguanine, procarbazine, lomustine and hydroxyurea) to increase tumor cell kill and, hopefully, to reduce repair of DNA damage. The therapy was active against previously treated recurrent anaplastic glioma, but less so against glioblastoma [77]. More recently, another combination chemotherapy protocol was developed called TCCC (6-thioguanine, lomustine or temozolomide, capectabine, celecoxib), designed to be used for patients failing either temozolomide (lomustine arm) or lomustine (temozolomide arm). The vast majority of patients were treated on the lomustine arm and, like the prior TPCH therapy, glioblastoma patients did not do as well as the anaplastic glioma patients who had combined response and stable disease rate of 68% with a PFS at 12 months of 44% [78].

Association of certain genetic abnormalities and response to chemotherapy

O(6)-methylguanine-DNA methyltransferase (MGMT) is a DNA repair enzyme that is frequently up-regulated in gliomas, rendering alkylating treatment insufficient [79]. Methylation and silencing of MGMT promoter may be a favorable prognostic factor in patients with glioblastoma treated with alkylating agents [80]. Thus, in glioma patients if antiepileptic medication is needed, use of levetiracetam, a potent inhibitor of MGMT, may sensitize glioma cells to alkylating agents [81]. Furthermore, clinical trials to deplete MGMT by O-6-benzylguanine, a noncytotoxic substrate of this enzyme, in combination with alkylating agents are in progress [82, 83].

In tumors of oligodendroglial origin, the -1p/-19q genotype may predict response to cytotoxic chemotherapy and favorable outcome [84]. However, the presence of polysomy for chromosomes 1 and 19 in anaplastic oligodendrogliomas with concurrent deletion of 1p/19q is a marker of early recurrence [85]. Irinotecan as single agent in patients with recurrent, TMZ-refractory, 1p19q co-deleted, anaplastic oligodendroglioma showed only modest effect [86], but improved activity with a combination of bevacizumab and irinotecan [87], or bevacizumab alone [88].

Future directions

Use of various dietary and nutraceutical approaches in patients with gliomas as adjuncts to standard therapies might prove to be beneficial for patients with recurrent gliomas. These agents include certain natural dietary components such as phytoestrogens and flavonoids, methionine restriction which may modulate MGMT activity and polyamine activity, anti-inflammatory drugs, and certain polyunsaturated fatty acids such as gamma-linolenic acid (GLA) that may exert antineoplastic activity against gliomas without harming normal cells [89]. For example, intratumoral administration of GLA in nine patients with recurrent GBM showed some effect and no significant side effects, suggesting that high doses of GLA should be investigated in subsequent studies [90]. Similarly, eflornithine (DFMO), an irreversible inhibitor of ornithine decarboxylase, the first enzyme in polyamine synthesis, has shown activity against gliomas as a single agent and in combination with cytotoxic drugs [91–93]. In patients with recurrent glioma and epilepsy, a combination of chemotherapy with antiepileptic drugs that demonstrate antineoplastic activities might offer an additional benefit [94].

Other potential useful approaches may include use of dendritic cell vaccines [95], gene therapy, virotherapy or stem cells as adjuncts to conventional therapies for gliomas [96]. Replication-incompetent or competent viruses can be used either as gene delivery vehicles to gliomas or to induce oncolysis and avoid damage of the adjacent normal cells [96, 97]. A similar approach consists of the use of stem cells for more efficient delivery of genetic material to glioma cells. Continuing research in the improvement of gene transfer efficiency and stem cell technology may overcome various safety issues and open new avenues in the management of gliomas in the future.

Conclusion

The management of newly diagnosed malignant gliomas include maximal surgery, postoperative radiation therapy

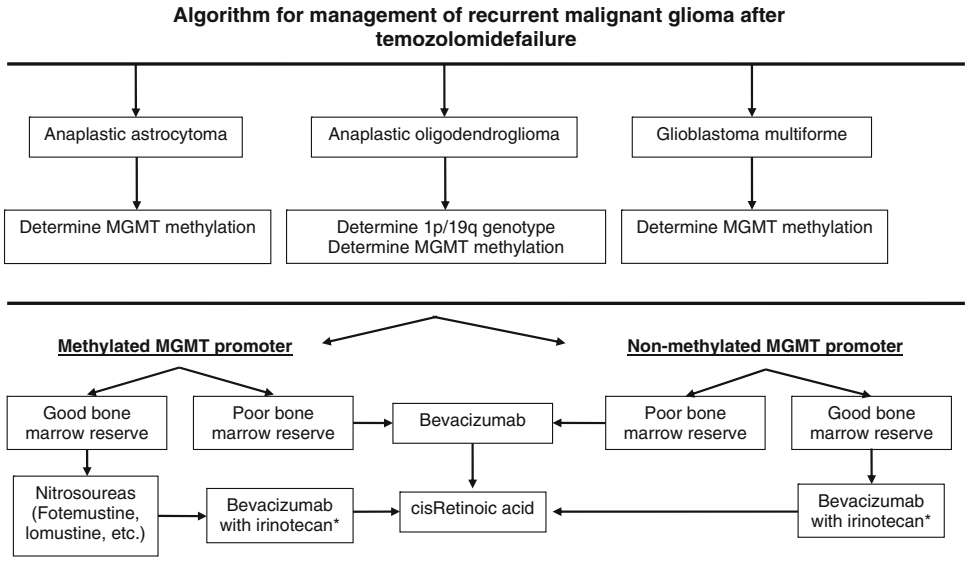

Fig. 1 Algorithm for management of glioma recurrence after initial surgery, radiotherapy and temozolomide chemotherapy. Determination of 1p/19q genotype status in patients with tumors of oligodendroglial origin may aid in prognosis determination. MGMT: O(6)-methylguanine-DNA methyltransferase; *asterisk* irinotecan or other cytotoxic agents as evidence develops from ongoing phase II trials

and, commonly, adjuvant chemotherapy with TMZ. At recurrence, patients who did not receive adjuvant TMZ chemotherapy should probably receive a TMZ-based chemotherapy. Based on our personal objective evaluation of the published phase II trials, for patients who do not participate in phase II trials, we recommend the following chemotherapies after TMZ failure in order of priority (Fig. 1): in patients with adequate bone marrow reserve and methylated MGMT status (likely sensitive to alkylating agents), nitrosourea (fotemustine, lomustine), bevacizumab/irinotecan and cis-retinoic acid. In patients with poor bone marrow reserve and methylated MGMT status, bevacizumab alone should be used followed by cis-retinoic acid. In patients with adequate bone marrow reserve and unmethylated MGMT (likely resistant to alkylating agents), bevacizumab/irinotecan followed by cRA, although TPCH or TCCC-like treatments might still have activity in about 30% of patients [77], could be used. In patients with poor bone marrow reserve and unmethylated MGMT, bevacizumab alone followed by cis-retinoic acid is recommended. Future studies employing dietary and nutraceutical approaches, tumor vaccines, gene therapy, virotherapy and stem cells may prove to be useful as adjuncts to standard chemotherapies to improve therapeutic benefit and prolong survival.

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