REVIEW

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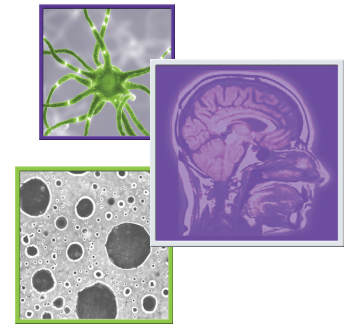

Treatment options for recurrent high-grade gliomas

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Practice points

- Likelihood of tumor recurrence after initial aggressive treatment of glioblastoma (GB) is very high.
- Although a standard treatment regimen exists for newly diagnosed GB, no such regimen is yet fully established for recurrent GB.
- Evidence that re-resection of recurrent GB improves overall survival varies widely.
- Bevacizumab, a monoclonal antibody that has been efficacious in other cancers, is believed to be well tolerated when utilized for recurrent GB and may improve outcomes.
- EGRF-targeted therapies and novel immunotherapeutic approaches have been investigated for recurrent GB management.
- Challenges contributing to GB tumor recurrence include tumor heterogeneity and proximity to eloquent brain locations.
- Future experimental trials may shed light on more robust therapeutic agents for this aggressive brain tumor with a high proclivity for recurrence.

High-grade gliomas are aggressive brain tumors encompassing Grade III and IV classifications. Of these, glioblastoma (GB) is the most malignant with a high rate of recurrence after initial resection. Although standard treatment does exist for newly diagnosed GBs, therapeutic strategies for recurrent GB are less solidified. However, mounting evidence describes the role of re-resection, bevacizumab, chemotherapy, targeted molecular therapies, immunotherapeutic approaches and radiotherapy in recurrent GB management. This review article provides analysis of the aforementioned therapies, through assessing their effect on overall survival. Because GB tumor heterogeneity is prevalent there is a constant need to investigate therapies targeting recurrence. Studies evaluating both therapeutic targets and strategies for high-grade gliomas are and will remain invaluable.

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Background

Primary tumors of the CNS affect nearly seven out of 100,000 people worldwide [1]. Of these tumors, tumors of glial origin are the most common. These glial tumors, referred to as gliomas, are classified into four histological tumor grades that play a large role in dictating treatments and prognoses. High-grade gliomas (HGGs) encompass the WHO classification of Grade III

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gliomas (anaplastic astrocytomas and anaplastic oligodendrogliomas) and Grade IV gliomas that are more rapidly-growing and aggressive as compared with their lower grade counterparts. Specifically, glioblastoma (GB) are the most malignant glioma tumors and represent 15–20% of all primary intracranial tumors [2].

Presenting clinical history of HGGs usually spans <3 months in more than one-half of affected patients. Common presenting symptoms are consequences of increased intracranial pressure secondary to tumor growth, and include headaches, cognitive impairment, seizures and focal neurological deficits. The standard treatment regimen for GB, as established by a Phase III randomized trial, consists of maximal surgical resection and radiotherapy in combination with temozolomide (TMZ) chemotherapy, followed by adjuvant TMZ for 6–12 cycles [3–5]. Regardless patients have a mere median survival of 14 months despite surgery, radiation and chemotherapy, as well as a 5-year survival rate of <10%, because of GB invasiveness and resistance to treatment [6]. This dismal prognosis is due to the invasive tumor cells, and signaling pathway analyses have implicated Akt activation with tumorigenicity and invasiveness, and Erk activation with GB cell proliferation, highlighting the potential role of concurrent inhibitory therapy [7].

Nearly all patients with GB suffer from tumor recurrence despite initial aggressive treatment [8]. Studies have shown the mean time to GB recurrence is approximately 32–36 weeks after initial multimodal treatment, and this is most frequently a result of continuous neoplastic growth within 2–3 cm from the original neoplasm [9].

This article aims to review current evidence regarding the treatment options for recurrent HGGs, in particular Grade IV GB tumors, with the goal of analyzing not only well-known therapeutics but also relatively novel agents that have been investigated. Furthermore, since standard treatment for recurrent GB is yet to be definitely established, this article will present treatment strategies for these aggressive brain tumors displaying high rates of regrowth. Although determining optimal management of patients with recurrent GB is certainly an evolving challenge, it is our hope that this review solidifies understanding of current treatment regimens and also propels the consideration and development of future therapeutic agents targeting GB progression.

Repeat surgical resection

Although it is well understood that re-resection for recurrent HGGs certainly provides relief of progressive symptoms, evidence of its specific impact on overall survival (OS), defined as the percentage of patients in a treatment group still alive for a given period of time after diagnosis, varies widely. A recent systematic review examining the benefit of repeat surgery for GB analyzed 31 studies and concluded that re-resection as described by 29 of these studies demonstrated survival benefit [10]; a time interval of >6 months between operations and Karnofsky Performance Score (KPS) >70 contributed to increased survival rates (KPS is a functional impairment index ranging from 0 to 100 that can assess patient prognosis). Approximately 25% of patients with recurrent GB can be considered candidates for surgical re-resection, subject to specific characteristics indicative of a favorable prognosis for reoperation. Currently, age <70 years, tumor volume <50 cm^3 and a preoperative KPS of >80% have been shown increase likelihood of survival time prolongation after reoperation [11–14].

Despite the information above, there is currently no consensus regarding the role of re-resection for recurrent HGGs certainly provides relief of progressive symptoms, evidence of its impact on OS varies widely. There is currently no consensus in the literature regarding the role of reoperation for recurrent GB. A recent retrospective analysis of 102/232 patients (44%) with recurrent GB who had undergone reoperation followed by chemotherapy revealed no significant benefit of surgery as compared with chemotherapy alone as measured by progression-free survival (PFS) [15]. In another retrospective analysis, OS of 20 patients with recurrent GB who had received only surgical re-resection or re-resection combined with chemotherapy and radiotherapy was assessed. Nine out of 20 patients (45%) who have received only repeat surgery for recurrence showed significantly lower survival rates as compared with the other 11 patients who had repeat surgery followed by radiosurgery or chemotherapy [16].

Analysis has also been performed evaluating the impact of extent of resection (EOR) at both initial and repeat resection of GB on OS. The sample size of patients studied was large, at 107 patients and univariate and multivariate analysis revealed that OS was maximized following re-resection if gross-total resection (GTR) was achieved upon reoperation regardless of

EOR status on the initial surgery [17]. Therefore it was postulated that repeat surgical resection of recurrent GB should be pursued if subtotal resection was initially performed and if there is a possibility of GTR at recurrence. Another study analyzed the survival advantage of EOR in patients undergoing re-resection for recurrent GB, and noted that such advantage was noticed with as little as 80% EOR [18]. It is important to note that although survival generally appears to be increased in patients undergoing resection for GB, the lack of randomized trials makes it difficult to objectively evaluate its efficacy.

Bevacizumab

A contributing reason driving GB recurrence and poor prognosis is its highly angiogenic nature as evidenced by microvascular proliferation and elevated expression of VEGF. Bevacizumab is a human recombinant monoclonal antibody to VEGF and a mediator of tumor angiogenesis that has been shown to have treatment efficacy in a number of cancers including metastatic breast and colorectal cancers [14,19,20]. Bevacizumab was initially evaluated in HGGs in combination with irinotecan, a topoisomerase I inhibitor, because studies had shown addition of bevacizumab to standard chemotherapy for patients with metastatic colorectal cancer prolongs PFS [21]. Bevacizumab received expedited US FDA approval in the USA in 2009 for treatment of recurrent GB and is available in most other countries worldwide other than the EU. Approval was based upon prospective Phase II trials [22,23]. In the first Phase II trial of bevacizumab and irinotecan for recurrent GB, 20/35 (57%) of patients had a partial radiographic response (the primary end point of the study) and the PFS at 6 months was 46% [24]. The second Phase II trial, termed the Brain Study, assessed bevacizumab's effect alone or with irinotecan in recurrent GB therapy. In the bevacizumab-alone and the bevacizumab-plus-irinotecan groups, 6 month PFS rates were 42.6 and 50.3%, respectively; objective response rates were 28.2 and 37.8%; and median OS times were 9.2 and 8.7 months [22].

Following these data, the FDA approved bevacizumab monotherapy for recurrent GB in patients who had undergone prior chemoradiotherapy. It is important to note that bevacizumab monotherapy has been shown to be well tolerated in patients with recurrent GB, more so than combination therapy. In the Phase II Brain study, rates of adverse events in patients undergoing monotherapy as compared with patients treated with irinotecan and bevacizumab were 46 and 66%, respectively [22].

In order to shed light onto which patient conditions may be most favorable to bevacizumab therapy, a retrospective analysis compared the outcomes of recurrent GB patients treated with bevacizumab to those in a control group. In patients >55 years of age, bevacizumab treatment reflected a significant increase in PFS and OS as compared with the control group, even though no outcome differences were observed in patients <55 years of age [25]. The authors postulated that perhaps there is an age-dependent response in recurrent GB in relation to VEGF-expression levels, propelling bevacizumab to work better in elderly populations. Although no certain biomarkers exists for patients responsive to bevacizumab, it appears there is robust management potential for patients with highest GB-related mortality – the elderly.

The first randomized controlled Phase II trial of bevacizumab therapy in recurrent GB, called the Dutch BELOB trial, as well as the EORTC 26101 trial, has prospectively evaluated its efficacy versus CCNU monotherapy (lomustine) and combination therapy (lomustine is an alkylating nitrosourea compound that has decent penetration across the blood–brain barrier [BBB]). The BELOB trial was performed across 14 hospitals in The Netherlands and targeted 148 patients with recurrent GB after TMZ-chemoradiotherapy. Dual therapy with bevacizumab and CCNU was compared with monotherapy of each, with 9 month OS being the primary assessed outcome [26]. It turned out that OS was lowest in the bevacizumab monotherapy group (38%) as compared with 43% for the lomustine group. Most impressively, patients who had undergone dual therapy had OS of 63%. The conclusion was reached that combination therapy with bevacizumab and CCNU for recurrent GB may prove most efficacious in prolonging OS, and that the future of bevacizumab monotherapy may be less certain. Despite these promising results, the combination of bevacizumab and lomustine for treating first recurrences of GB did not improve OS in the subsequent Phase III EORTC-26101 trial, reported at the *20th Annual Scientific Meeting of the Society for Neuro-Oncology*, held on 19–22 November in San Antonio, TX, USA. PFS seemed promising, 4.17 months among

patients receiving the combination treatment versus 1.54 months among controls receiving only lomustine (hazard ratio [HR]: 0.49; 95% CI: 0.39–0.61; p < 0.0001). A total of 8.8% of patients in the combination-therapy arm had no progression at 1 year, compared with 19% of patients in the lomustine-alone arm [27]. However, OS did not differ between the two study arms, with a median OS of 8.6 months for the lomustine-alone study group and 9.1 in the bevacizumab/lomustine study group (HR: 0.95; 95% CI: 0.74–1.21; p = 0.65). Nor was neurological deterioration-free survival significantly different between the lomustine and the bevacizumab/lomustine study arms (5.72 vs 6.21 months, HR: 0.78; 95% CI: 0.58–1.06; p = 0.112) [27]. Toxicity was as expected, with more myelosuppressive events in the combination arm. Crossover to bevacizumab occurred in 35.5% of patients in the control arm, whereas 19% of patients in the combination arm continued with bevacizumab at progression. Epigenetic classifcation, *MGMT* status and other expression profiling data analyses will be reported in the near future.

In summary, whereas bevacizumab seems to result in improvements in recurrent GB PFS secondary to microvascular regression, improvements in OS appear to be limited [28]. One study has indicated that vascular modeling induced by repetitive bevacizumab treatments may actually lead to a hypoxic neoplasm environment that propels glycolysis and ultimately leads to tumor cell invasion [29]. This indicates the possible need to combine bevacizumab therapy with drugs that target the glycolysis pathway in order to ensure that tumor growth regresses rather than progresses due to further invasion after treatment. Further validation of such molecular markers may lead to more explicit stratification of treatment strategies recurrent GB patients.

Salvage chemotherapy

In addition to pursuing re-resection and/or bevacizumab therapy as management strategies for recurrent GB, utilization of salvage chemotherapy has also been investigated extensively. A prospective Phase II study analyzed efficacy of CPT-11 monotherapy administration in 40 adult patients (median age: 59) who were treated with two cycles of CPT-11, a topoisomerase I inhibitor chemotherapy agent, following diagnosis of tumor progression [30]. The patients were then evaluated with MRI and thorough neurological examinations. Although no treatment-related deaths occurred, there was a lack of response in the CPT-11 patient group with recurrent GB. It is necessary to note that perhaps a longer CPT-11 cycle schedule would be more conducive toward drawing conclusions toward its efficacy, as each cycle lasted only 3 weeks in duration. To address this point, a study over a longer period of time was conducted in which 38 adults (median age: 52 years) with GB and KPS >60 with recurrent disease were given CPT-11 with the goal of determining PFS-6 as a means of concluding if CPT-11 treatment could significantly delay tumor progression [31]. PFS-6 was a mere 15.7% in the recurrent GB patients treated with CPT-11 for 6 months, and it was concluded that CPT-11 administration was not efficacious over this long-term schedule.

Since the approval of TMZ in 1997 for high-grade glioma treatment, it has become the current chemotherapeutic agent used prevalently for newly-diagnosed GB patients, with standard treatment being favorably composed of concomitant chemoradiotherapy (CCRT) with TMZ followed by six cycles of adjuvant TMZ [5]. It is important to highlight that TMZ, the most widely utilized alkylating agent in GB, induces DNA damage and cell death. For a subset of GBs, the protein O^6-MGMT promoter is methylated, enhancing chemosensitivity. Studies have shown that MGMT is unmethylated in approximately 60% of GBs, thus providing inherent resistance to alkylating agents [5,33]. Salvage chemotherapy with TMZ monotherapy for recurrent GB has also been studied extensively in an attempt to determine the best treatment for recurrent GB. A recent retrospective analysis published in 2015 analyzed 144 patients who had initially received maximal surgical resection combined with CCRT and adjuvant TMZ and eventually suffered from recurrent GB. Out of these patients, 31 patients (22%) underwent solely salvage treatment, 28 (20%) had dual therapy with Gamma knife radiosurgery (GKS) followed by TMZ and 38 (26%) underwent surgical re-resection [32]. The median OS of the TMZ, GKS + TMZ and reoperation groups were 5.6, 15.5 and 13.2, respectively, and median PFS were 2.3, 6.0 and 4.3. It was concluded that, when assessing the role of TMZ in treatment for recurrent GB, GKS + TMZ treatment would be most efficacious.

TMZ rechallenge as the salvage treatment for recurrent GB has also been favorably supported

by a recent study in which investigators utilized continuous TMZ, termed 'TMZ rescue', at time of progression followed by CCRT and conventional TMZ [33]. In this study, the PFS-6 was 57% with limited toxicity. An additional study by Wick *et al.* in 2009 evaluated TMZ rechallenge as sole treatment for GB recurrence and concluded that TMZ generated promising PFS-6 results in patients who had experienced GB recurrence over an unspecified period of time [33]. Numerous trials have also analyzed TMZ efficacy as monotherapy for progressive HGGs. Studies administered TMZ in traditional 5-day cycles after diagnosis of recurrence, and across all studies, PFS-6 averaged 33% and median OS 7.7 months [34,35]. A Phase II trial was also performed to evaluate efficacy of dose-dense TMZ for patients with recurrent HGGs, specifically consisting of 7 days on and 7 days off of treatment [36]. Among the patients with recurrent GBs, PFS-6 was 10% with an OS of 21.6 weeks and although the dose-dense TMZ alternative treatment was well tolerated it was not reported to have significant activity in the patient population.

Overall, it appears that further studies of CPT-11 use in recurrent GM are required to better understand its efficacy in high-grade glioma management. Furthermore, as mentioned above, ample evidence has highlighted the beneficial role of Gamma knife radio surgery and combination TMZ therapy in recurrent glioma therapy. It is particularly important to note that MGMT promoter methylation appears to be a predictive biomarker of radiation response to alkylating agents including TMZ, and therefore may influence therapy decisions for patients.

Targeted molecular therapies

Although there exists genetic heterogeneity among individual HGGs, a number of common molecular pathways have been identified to be upregulated and responsible for driving tumor propagation and invasiveness. These molecular pathways have been targets for novel small molecule inhibitors in attempts to reverse these aggressive phenotypes. For example, EGFR is amplified in over 50% of GBs. About 40% of GBs with EGFR amplification express mutant receptor EGFRvIII that has been shown to be an independent prognostic factor for poor OS [37]. Accordingly, EGFR-targeted therapies have been developed for management of recurrent GB, including gefitinib (Iressa) and erlotinib (Tarceva), although these have not yet proved to be successful.

A Phase II study of geftinib for recurrent GB reported a PFS-6 of 17%, which was the same as in historical controls [37]. Other Phase II studies by the North Central Cancer Treatment Group failed to reveal any survival benefits in patients who were administered gefitinib for recurrent GB [38]. A Phase I trial analyzing the use of erlotinib monotherapy to treat GB progression demonstrated a PFS-6 of 11% but with modest impact on OS [39]. More recently, a large randomized Phase II study by the EORTC compared erlotinib with TMZ for recurrent GB and found the results disappointing when the EGFR inhibitor was used as monotherapy. These series of trials highlight that such EGFR-targeted therapies have unclear impact on long-term survival.

The PI3K/AKT/mTOR intracellular signaling pathway has also been investigated as a means of targeted molecular therapy. A preclinical study revealed that inhibiting PI3K may decrease TMZ resistance by enhancing cytotoxicity and increasing suppression of cellular proliferation [40]. This pathway is currently being analyzed further as a targeted molecular therapy for recurrent HGGs.

Oncolytic viral (OV) therapies are also a promising component of the GB treatment repertoire. As compared with gene therapy, in which the role of therapeutic genes is of utmost importance, oncolytic virotherapy utilizes viruses with a preserved potential for the active viral cycle. Fifteen of such viruses have been tested on GB, and 20 clinical trials have been implemented [41]. Four oncolytic strains have completed Phase I clinical trials in GB patients targeting safety. Among 120 GB patients treated with OV, there was near complete absence of serious adverse events. Further studies are needed to more thoroughly investigate the role of OV therapy in management of HGGs.

Immunotherapy

Immunotherapy represents a promising avenue for cancer therapy given its potential for its specificity for cancer cells while minimizing systemic toxicity. Heat shock protein (HSP) has been one such approach against GB. HSPs are chaperone proteins transcriptionally unregulated in cancers including HGGs, in which there is increased translation of abnormal protein products. Specifically, in GB there is heightened transcription of HSP70 mRNA and HSP90 has been

shown to regulate tumor propagation signaling pathways implicated in GB [42]. HSP-peptide based vaccines have been derived from the isolation and purification of HSPs from resected GB patients following reinfusion of the complex, enabling the chaperone proteins to interact with antigen presenting cells and ultimately train naive immune cells against antigenic targets. Phase I, II and III clinical trials have been conducted to investigate HSP vaccines, with the majority of HSP vaccine trials having studied HSP peptide-complex 96 (HSPPC-96). A recent Phase II study targeted 41 patients with recurrent GB who had received GTR followed by HSPPC-96 vaccine doses, with the primary end point being PFS-6. Survival data was quite promising, with 90.2% of the patients alive at 6 months, with median survival being nearly 43 weeks [43]. HSPPC-96 warrants further study as an appropriate, efficacious immunotherapy for recurrent GB.

Two novel immunotherapeutic approaches for recurrent GB have recently emerged as safe and auspicious, namely Rintega and DCVax-L. Developed by Celldex Therapeutics, Rintega consists of an EGFRvIII peptide that generates a targeted immune response against EGFRvIII-expressing recurrent GBs. A randomized controlled Phase II exploratory study, coined the ReACT study, revealed dual therapy with Rintega and bevacizumab demonstrated a statistically significant and clinically meaningful benefit in OS as compared with bevacizumab monotherapy for GB progression. PFS-6 of Rintega + bevacizumab groups was 30%, as compared with a mere 12% for bevacizumab montherapy groups [44]. In addition, a Phase III study called ACT IV was conducted in newly diagnosed EGFR*vIII*-positive GB patients. The 745 patient study was a randomized, double-blind, controlled study of RINTEGA plus granulocyte-macrophage colony-stimulating factor added to standard of care TMZ. The control arm regimen included standard of care TMZ plus injections of keyhole limpet hemocyanin, which is a component of RINTEGA and was selected due to its ability to generate an injection site reaction similar to that observed with the RINTEGA vaccine, which improves the blinding of the study. The ACT IV study was discontinued in March 2016 based on the recommendation of the independent data safety and monitoring board that the study was unlikely to meet its primary OS end point in patients with minimal residual disease as both the RINTEGA arm and the control arm were performing on par with each other. In the ACT IV study, RINTEGA performed consistently with prior Phase II studies (ACTIVATE, ACT II, ACT III) but the control arm significantly outperformed expectations (hazard ratio = 0.99; median OS: RINTEGA 20.4 months vs control 21.1 months). Across all studies, RINTEGA has been generally well tolerated. The most common adverse events are injection site reactions, fatigue, rash, nausea and pruritus.

DCVax-L is a dendritic cell-based vaccine composed of autologous dendritic cells paired with tumor lysate [45]. Two Phase I and II trials have been completed and a Phase III trial is ongoing. The completed trials were composed of 20 patients with newly diagnosed GB as well as 19 patients with recurrence. A total of 33% of the recurrence patients had reached or exceeded median survival of 4 years, and 27% had exceeded that of 6 years. This was perceived as quite efficacious considering the grim prognosis of GB, with its median survival of only 14 months even after combination surgical resection, chemotherapy and radiotherapy. Currently the 348 patient Phase III clinical trial for DCVax-L is being carried out in order to assess PFS-6, and the results will likely play a major role in molding the future of this vaccine into the realm of recurrent GB management.

Mutations in isocitrate dehydrogenase (IDH) has been identified as an early molecular event in GB proliferation, and IDH1 mutations have been associated with favorable outcomes in Grade III and IV malignant tumors [2]. In 2008, The Cancer Genome Atlas conduced genome-wide analyses that, for the first time, identified mutations of the IDH1 gene in GB tumor samples [46]. Recent attempts have been made to develop vaccine immunotherapies targeting the IDH1 mutation protein [47]. Currently, two Phase I trials investigating the role of oral therapy in targeting the IDH1 mutant protein in patient with GB are underway with interim results pending.

Radiotherapy

Salvage radiotherapy has also been extensively investigated as a therapeutic option for GB progression, specifically for a small minority of patients with focal disease. First conceived in 1951, stereotactic radiosurgery is an irradiation mechanism enabling delivery of large radiation doses to a small target tumor site via high energy

radiation beams. Several retrospective analyses have highlighted its specific benefit as an alternative to surgical resection for surgically inaccessible and progressive HGGs including GB. For instance, one study reported salvage radiotherapy as having superior local tumor control rates as compared with reoperation for recurrence [48]. A recent retrospective analysis compared 29 patients who had received Gamma knife monotherapy for recurrent GB with 28 patients who had received dual therapy with GKS + TMZ [32]. Median OS of the GKS and GKS + TMZ groups was 9.2 and 15.5, respectively, and median PFS was 3.6 and 6.0. It was therefore concluded that dual therapy consisting of GKS + TMZ would be more likely to enhance survival.

Linear accelerator-based radiosurgery has been utilized for treatment of HGGs and data have been reported on 86 patients who underwent it after recurrence [49]. Patients with tumors smaller than 10.1 cm^3 who underwent this therapy experienced median survivals of 15.1 months as compared with 8.1 months in patients with bigger GBs. In the absence of randomized evidence, it is challenging to determine whether stereotactic radiosurgery improves OS in recurrent GB, but evidence has shown that salvage radiotherapy, particularly in conjunction with chemotherapy, may be efficacious for management of recurrent HGGs.

Intratumoral injection

In most cases, the delivery of adequate drug concentration to recurrent GBs is anatomically challenging due to difficulty traversing the BBB. Convection-enhanced delivery (CED) has been investigated as a loco-regional delivery mechanism by which pharmacological agents can bypass the BBB and be used for recurrent GB treatment. Specifically, drug delivery occurs via catheters placed directly within the tumor mass or around its cavity, allowing the infusate to be administered into the brain tissue. The first Phase III trial for CED, known as the PRECISE study, compared OS and tolerability of cintredekin besudotox

Box 1. Summary of various treatment strategies for recurrent high-grade gliomas.

Repeat resection
- 25% of patients with recurrence can be considered candidates for re-resection
- 102/232 patients (44%) with recurrence undergoing re-resection + chemotherapy showed no PFS benefit of sole surgery as compared with chemotherapy alone
- If re-resection is pursued, overall survival correlates with EOR

Bevacizumab
- Phase II trial: monotherapy –> PFS-6 of 43%; combination therapy with irinotecan –> PFS-6 of 50%
- BELOB Trial: OS for monotherapy 38 vs 43% for combination therapy with CCNU

Salvage chemotherapy
- CPT-11 for 6 months: PFS-6 15.7%
- TMZ+GKS OS 15.5 vs TMZ monotherapy OS 5.6
- Dose-dense TMZ treatment: well tolerated but without significant benefit

Targeted molecular therapies
- Phase II trial geftinib: PFS-6 17%
- Phase I trial erlotinib: PFS-6 11%, modest impact on OS
- PI3K inhibition may decrease resistance against TMZ

Immunotherapy
- HSPPC-96: PFS-6 90%, median survival 43 weeks
- ReACT: PFS-6 Rintega + bevacizumab 30 versus 12% for Bevacizumab
- monotherapy
- DCVax-L: Phase III trial is ongoing

Radiotherapy
- GKS + TMZ OS 15.5 versus TMZ monotherapy OS 5.6

Intratumoral injection
- PRECISE study for convection-enhanced delivery:
  - Cintredekin besudotox + Gliadel (BCNU) was well tolerated yet exhibits limited survival difference

EOR: Extent of resection; GKS: Gamma knife radiosurgery; OS: Overall survival; PFS: Progression-free survival; TMZ: Temozolomide.

(CB) via CED versus the surgical implantation of Gliadel Wafer. CB is composed of human IL-13 and recognizes tumor cells that express this receptor to induce apoptosis. As the majority of HGGs overexpress IL-13 receptors, this therapeutic has the capacity to directly target recurrent GB tumors. The Gliadel (BCNU) wafer is an antineoplastic drug approved by the FDA for treatment of GB progression. Results of the trial revealed that administration of both CB and the Gliadel wafer were well tolerated by patients and that a limited survival difference was evident among the two different CED agents [50]. For the efficacy evaluable population, the median survival was 45.3 weeks for CB cohort and 39.8 weeks for Gliadel ($p = 0.310$). It is important to note that drug distribution was not assessed in this trial for either agent.

In a mouse model of GB, one group injected lipopolysaccharides into the tumors and assessed for regression, with the proposed mechanism that lipopolysaccharides induce strong immune responses that may prevent cellar proliferation of malignant gliomas. Specifically, complete or nearly total tumor regression was achieved in 20/20 (100%) of mice injected with 400 mg of lipopolysaccharides [51]. Although this has not yet been investigated in humans, it nevertheless is a very exciting finding highlighting its possible antitumoral effects on GB.

Future evaluations of CED-based therapeutics will inevitably benefit from drug distribution assessment and real time imaging capability allowing the investigator to image whether the drug is hitting its target.

Conclusion

Management of recurrent HGGs including GM is challenged by multiple factors including tumor heterogeneity and proximity to eloquent locations that make it difficult for maximal initial surgical resection **(Box 1)**. These factors increase the propensity toward developing recurrence. The future will be exciting to see whether imaging biomarkers and next generation sequencing can continue to facilitate the discovery of therapeutic targets and strategies for recurrent HGGs. Ultimately, the final decision regarding course of treatment for recurrent GB should factor in specific patient characteristics, and patients should be presented with the opportunity to participate in experimental trials which will inevitably help develop both current and future therapeutic agents for this aggressive brain tumor with grim prognosis.

Future perspective

Although it is largely accepted that maximal surgical resection, radiotherapy and concomitant and adjuvant TMZ is the standard of care for patients with newly diagnosed GB, therapeutic strategies for recurrent GB are less established. This is of particular concern considering that even with initial treatment, the prognosis of HGGs including GB is dismal, with a median survival of only 14 months and a high rate of recurrence. Even though treatment for recurrent HGGs is a constantly evolving challenge, the aforementioned therapies – which range from resection to chemotherapy to CED – all offer glimpses of hope by revealing that increased understanding of molecular mechanisms paired with clinical trials have led to auspicious therapeutic approaches.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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