Review

Management of glioblastoma after recurrence: A changing paradigm

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KEYWORDS
Recurrent; Glioblastoma; Re-irradiation; Bevacizumab; Chemotherapy; NovoTTF

Abstract Glioblastoma remains the most common primary brain tumor after the age of 40 years. Maximal safe surgery followed by adjuvant chemoradiotherapy has remained the standard treatment for glioblastoma (GBM). But recurrence is an inevitable event in the natural history of GBM with most patients experiencing it after 6–9 months of primary treatment. Recurrent GBM poses great challenge to manage with no well-defined management protocols. The challenge starts from differentiating radiation necrosis from true local progression. A fine balance needs to be maintained on improving survival and assuring a better quality of life. Treatment options are limited and ranges from re-excision, re-irradiation, systemic chemotherapy or a combination of these. Re-excision and re-irradiation must be attempted in selected patients and has been shown to improve survival outcomes. To facilitate the management of GBM recurrences, a treatment algorithm is proposed.

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Contents

Introduction .................................................................................................................. 00
Search methodology ................................................................................................ .... 00
  Diagnosis of a recurrence .................................................................................... 00
  Selection of patients for retreatment ................................................................. 00
Surgical salvage .......................................................................................................... 00
Re-irradiation ............................................................................................................. 00
Chemotherapy ........................................................................................................... 00
  Bevacizumab ....................................................................................................... 00
  Nitrosoureas ....................................................................................................... 00
  Temozolomide ................................................................................................. 00
Novel treatment techniques .................................................................................... 00

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Impact of anti-epileptic drugs ................................................................. 00
Management of recurrent GBM in elderly and pediatric patients .......... 00
Quality of life ..................................................................................... 00
Future directions ............................................................................... 00
Conclusions ..................................................................................... 00
Disclosures ...................................................................................... 00
Meeting presentation ........................................................................ 00
Financial support ........................................................................... 00
Conflict of interest .......................................................................... 00
Levels of evidence ........................................................................... 00
References ....................................................................................... 00

Introduction

Glioblastoma (GBM) is the most common primary brain cancer in the age group after 40 years and the prognosis gets worse as the age increases. The land mark trial by Stupp et al. led to acceptance that maximal safe surgery followed by adjuvant chemoradiotherapy and adjuvant chemotherapy to be the standard of care [1]. But local infield recurrence is an inevitable event, with most patients experiencing it after 6–9 months of primary treatment because of resistant GBM stem cell and neuronal stem cells, suboptimal mean dose to the ipsilateral subventricular zone (SVZ) or involvement of corpus callosum [2,3]. Different molecular factors like P53 mutation, MIB-1 labeling index, and O-6-methylguanine-DNA methyltransferase (MGMT) methylation have been correlated with recurrence in GBM [4,5]. The various radiation treatment protocols with dose escalation beyond 60 Gy have been unsuccessful and have led to increased toxicity. There has been much controversy in the diagnosis of recurrence with the definitive diagnosis only via histopathological examination. But most of the patients with imaging finding suggestive of progression may not be fit for a surgical procedure, making the diagnosis of recurrent GBM difficult. The main differential diagnosis includes radiation necrosis which also occurs at the same time period and may be symptomatic thus mimicking progression. But the recent advances in imaging have helped us in a great way in differentiation between the two. The treatment of recurrent glial tumors has always been challenging and is associated with significant toxicities and always a balance has to be achieved between local control and treatment related morbidities and mortalities [6,7].

Surgery remains an important therapeutic strategy. However, only a small proportion of patients are found eligible for a total surgical resection. Re-irradiation (ReRT) has evolved as a salvage option in the last decade [8]. Evolution of new radiotherapy techniques and better image guidance may help in giving highly conformal doses and thus limiting toxicity. Chemotherapy has also been used by various groups with an aim to improve survival outcomes. But despite these various treatment options, outcome of these patients has remained dismal [9–11]. There has been some recent interest with some new modalities showing promising results available for some of these. But the presence of the blood–brain barrier (BBB) limits the delivery of most chemotherapeutic agents [12,13]. However, most of the treatment regimens have surfaced with single institute retrospective analysis or few phase II clinical studies. So, there hardly exists any standard treatment. In this review we intend to review available investigations for the diagnosis and treatment modalities with meaningful impact on survival and derive a possible therapeutic algorithm for patients with recurrent GBM.

Search methodology

We searched the PubMed for literature of recurrent glioblastoma. We used the following MeSH terminology: recurrent glioblastoma retrieved 2023 entries; recurrent glioblastoma AND treatment retrieved 1775 entries (4 phase III, 230 Phase II, 104 phase I study, 2-metaanalysis). We retrieved a total of 57 articles pertaining to recurrent glioblastoma AND reirradiation but none of these were a phase I/II study. Only 16 found to describe retrospective result of treating recurrent GBM with reirradiation. We also searched for recurrent glioblastoma AND surgery we retrieved 31 entries with one phase II study. There were 56 entries for the MeSH term of recurrent glioblastoma AND vaccine out of which only fourteen described a phase I/II study. 187 phase I/II and 2 phase III trials described chemotherapy/targeted therapy for rGBM.

Diagnosis of a recurrence

Diagnosing a recurrence in GBM patients remains a challenge with radio necrosis closely resembling changes of recurrence on imaging. Examination of the surgically resected specimen remains the gold standard for the diagnosis of radiation necrosis. The picture is in fact further complicated by coexistence of both in many cases. The new advances in radiology and nuclear medicine may help in some cases to differentiate these entities. A good clinical judgment along information from these various imaging modalities may help us in majority of the cases.

Combination of contrast enhanced (CE) T1-weighted imaging, diffusion-weighted (DW) imaging, and perfusion MR imaging resulted in significantly better diagnostic accuracy without much impact from selection of perfusion MR method (dynamic CE [DCE]) vs dynamic susceptibility CE) [14]. In magnetic resonance spectroscopy (MRS) tumor recurrence is characterized by a higher Choline (Ch)/N-acetylaspartate (NAA) and Ch/(creatinne) Cr ratio but a low NAA/Cr ratio. Lower lipid signals in MRS are also characteristic of tumor recurrence. Hence, the presence of elevated lipid signals along with low choline/NAA ratios may help to differentiate radiation changes from tumor recurrence [15]. Relative cerebral
Management of Glioblastoma after recurrence

Table 1  Comparison of imaging characteristics of Recurrent Glioblastoma vs. Radiation necrosis.

<table>
<thead>
<tr>
<th></th>
<th>Radiation necrosis</th>
<th>Glioma recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Magnetic Resonance Imaging- Suggestive features</td>
<td>• Usually in the areas of high dose (&gt; 60 Gray)</td>
<td>• Can occur anywhere, But infiel recurrence is the most common</td>
</tr>
<tr>
<td></td>
<td>• Contrast enhancement, edema, and mass effect may</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Classical Swiss cheese appearance</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Involvement of corpus-callosus or peri-ventricular white matter</td>
<td></td>
</tr>
<tr>
<td>Magnetic Resonance Spectroscopy [17]</td>
<td>• Low Cho/NAA &lt; 1.11</td>
<td>• High Cho/NAA &gt; 1.11</td>
</tr>
<tr>
<td></td>
<td>• Low Ch/Cr ratio &lt; 1.17</td>
<td>• High Ch/Cr ratio &gt; 1.17</td>
</tr>
<tr>
<td></td>
<td>• Elevated lipid signals</td>
<td>• Low lipid signals</td>
</tr>
<tr>
<td>Diffusion weighted magnetic resonance imaging [18]</td>
<td>• Higher apparent diffusion coefficient (ADC)-maxima ADC in range of 2.3</td>
<td>• Lower ADC values in range of 1.7</td>
</tr>
<tr>
<td>Perfusion magnetic resonance imaging [19]</td>
<td>• Cerebral blood volume (CBV) &lt; 0.6</td>
<td>• CBV usually more than 2.6</td>
</tr>
<tr>
<td></td>
<td>• Higher fractional anisotropy (FA) values- 0.89 ± 0.15</td>
<td>• Lower fractional anisotropy (FA) values- 0.74 ± 0.14</td>
</tr>
<tr>
<td>Positron Emission Tomography</td>
<td>• Low metabolic activity</td>
<td>• High metabolic activity</td>
</tr>
<tr>
<td>Single Photon Emission Computed Tomography</td>
<td>• Low metabolic activity</td>
<td>• High metabolic activity</td>
</tr>
</tbody>
</table>

blood volume (CBV) in perfusion images is also helpful to differentiate radiation necrosis and recurrence with a high relative CBV (more than 2.6) for tumor and low CBV (usually < 0.6) for radiation necrosis. Positron emission tomography (PET) image tumor shows more metabolic activity compared to radiation necrosis. However a low image resolution remains the limiting factor but this may be overcome with integration of MRI or computed tomography with PET scans. Tc-GH SPECT/CT is not inferior to F-FDOPA PET/CT for detection of recurrence and can be used as a low-cost alternative [16]. The radiological features of radiation necrosis vs. recurrence of tumor are summarized in Table 1.

Selection of patients for retreatment

A number of factors have been evaluated to correlate with the prognosis of patients [17-20]. In a recent review Weller et al. found Karnofsky performance score (KPS) > 60, tumor size < 4 cm and progression after > 6 months to confer better survival [20]. These factors may also be helpful in selecting suitable patients for treatment also. Those patients who have a young age, recurrence occurring after 6 months and with good performance status may be selected for an aggressive approach. Size of the lesion at the time of recurrence and presence of symptoms, may be also the factors taken into account when planning for an aggressive approach. Surgical approach helps in getting the final diagnosis and early relief of symptoms in the patient.

Surgical salvage

Surgery in recurrent GBM is aimed to reduce the tumor bulk and achieve symptom relief. It also helps us in the definitive diagnosis of a recurrence and repeat morphological and evaluation helps us in evaluating for tumor heterogeneity which is common in brain tumors. Salvage surgery alone has yielded short term disease control only and literature authors have found surgery to increase morbidity in a recurrent setting [20]. However, Bartsch et al. reported improved survival for patients treated with surgery as a component of the salvage therapy [21]. In a study by Sughrue et al. it was found that the median PFS was 7.8 months, 6.0 months, and 4.8 months following the second, third, and fourth-sixth craniotomies, respectively [22]. Bloch et al. reported median PFS after re-surgery: GTR 11.3 month’s vs. STR 6.7 months [23]. They found that age, performance status and extent of resection at repeat surgery to be significant factors influencing survival. Franceschi et al. in a recent series also failed to show a survival advantage with re-surgery [24].

In the earlier reported studies there was little agreement to the importance of surgery as salvage treatment and survival benefit associated with it. The tumor extension to eloquent areas and lack of intraoperative imaging were drawbacks in these series. However intraoperative neuro navigation and use of 5 Aminolevulinic acid (ALA) as guide to resect tumor helps in reducing the toxicity and improving the tumor control. The principles of surgery in recurrent setting must follow those of the upfront setting. A maximal safe surgery must be attempted and intra operative use of ultrasound and cavitron ultrasonic surgical aspirator must be encouraged. As the patients get symptom relief and are associated with improved survival surgical resection must be done in all patients found suitable based on available evidence. The added advantage is that a confirmatory diagnosis of tumor recurrence is got.

Re-irradiation

Re-irradiation may be done in patients with small volume recurrence, if far from the primary area of irradiation, if surgery is not possible due to eloquent location of the tumor. Another factor that should be assessed before re-irradiation is the time period of recurrence and first irradiation the longer the interval the better may be the outcome [25]. Re-irradiation...
have also been tried in surgery to improve outcomes and must be given to patients who are found suitable. The major issue with the use of radiation is the anticipation of debilitating toxicity in the form of radiation necrosis [25]. The radiation tolerance is the most important limiting factor [26]. However, in the last decade there was a paradigm shift in the understanding and practice of radiation for recurrent gliomas [26,27].

Re-irradiation may be done by external beam radiotherapy or by brachytherapy. Most of the published literature on re-irradiation has used external beam radiotherapy. Newer treatment techniques enable delivery of radiation more precisely to the target without crossing the tolerance of normal surrounding structure [10,28–30]. MRI, SPECT and PET images found are of real help for target delineation. Sminia et al. recently reviewed all published data of re-irradiation to compare the impact of conventional, stereotactic radiotherapy (SRT)/surgery (SRS) in the management of recurrent glioma [31]. The review compiled the published literature to show that across different re-irradiation series the dose prescribed ranged from 20 to 45.5 Gy with recurrence equivalent total dose (rEQD2) 30–51.3 Gy. The total equivalent radiation dose (EQD2) was 81.6–102.8 Gy. The PFS ranged from 6.2 to 27.5 months with maximum 6% radiation necrosis [31]. Radio-necrosis in retreated gial tumor is the most fearful complication. However, in the published literature only a handful of evidence exists reporting radio necrosis. The paucity of true incidence and its reporting can also be attributed to truncated follow up. Ramona Mayer et al. in a review correlated radiation necrosis to be commoner with normalized total dose of more than 100 Gy [25]. Survival after re-irradiation varies widely with a median DFS 7–9 months reported across the different studies. However, it should be noted that patient characteristic is variable in different cohorts.

The target volume is generally the contrast enhancing tumor volume that is contoured as the gross tumor volume (GTV). A 5 mm margin around the GTV is generally given to form the clinical target volume. Whenever possible the MRI of the patient must be fused to the planning CT for better target delineation. The dose to be prescribed must depend on various factors like time since the previous irradiation, volume of recurrence, location of recurrence and dose and fractionation used in the first plan. The other factor that should be taken into consideration when planning for re-irradiation is the proximity to the brain stem and optic structures. Generally the cumulative EQD2 is kept at around 100 Gy. The dose prescribed for re-irradiation in most of the studies has ranged from 30 Gy to 45 Gy. The dose prescribed should be individualized for each patient depending on the above mentioned factors.

Although re-irradiation can be tried after a time period of 6 months the ideal case would be a patient recurring after 2 years. The tolerance of various critical structures during re-irradiation is also an area of great concern and there is a lack of convincing data on the same. The tolerance of the critical structures like brain stem and optic structures is usually reached in the first irradiation. The recovery of these neural structures is not as other organs in the body and is limited. But there are animal models which have shown good recovery of these structures. Keeping a cumulative EQD2 of less than 80 Gy for the optic structures and EQD2 of 90 Gy for the brain stem would be logical for these patients, although convincing data are not available. The EQD2 for the rest of the brain may be kept below 90–100 Gy. But these should be individualized for each patient depending on various factors like dose and fractionation schedule of the first irradiation, time that has elapsed and presence of any radiation changes in imaging of these patients. This should also take into account the expected survival of these patients, as these patients with recurrent GBM are having very poor survival a more liberal risk of toxicity may be accepted in some patients.

The technique to be used for re-irradiation varies from 3d-conformal radiotherapy to intensity modulated radiotherapy. Most of the current published literature uses stereotactic techniques for re-irradiation of these patients. When using 3-D conformal techniques one should be careful to use a different field arrangement than the one used for initial irradiation. Generally intensity modulated radiotherapy with good immobilization is preferred for such patients. A summary of the major trials which have used external beam radiotherapy for re-irradiation is summarized below in Table 2. Brachytherapy is also being evaluated as a treatment option for recurrent GBM. In a large series Kickingeder et al. reported experience of treating inoperable primary and recurrent glioblastoma with low-dose rate stereotactic iodine-125 brachytherapy [30]. Median cumulative surface dose was 60 Gy; and median dose-rate 6 GY/h. In addition to brachytherapy, 90.3% of patients in the primary treatment group received external boost radiotherapy (median dose, 25.2 Gy) and 30.8% received adjuvant chemotherapy with Temozolomide being the most commonly used drug. The authors reported impressive 10.5 and 6.2 months median OS and PFS rates respectively and Karnofsky performance score, age, and adjuvant chemotherapy were reported as independent prognostic factors [30]. Archavlis et al. in another retrospective study compared high dose rate (HDR) brachytherapy to re-surgery and dose dense temozolomide for recurrent GBM patients. The HDR-brachytherapy consisted of an after loading 192Ir implant which delivered a median dose of 40 Gy [32–52] at twice-daily fractions of 5.0 Gy to a CT-MRI fusion-defined planning treatment volume. The authors reported a median survival 37, 30 and 26 weeks after salvage therapy of the recurrence was, respectively with no added complication in the HDR brachytherapy group [33].

There is no consensus on what technique is used in re-irradiation. The poor survival in these patients along with the invasive nature of brachytherapy leads to external beam radiotherapy being preferred by most. But brachytherapy is a very promising form of radiotherapy with good conformal dose distribution and may be tried in superficial tumors. But the lack of expertise is a major limiting factor.

The role of adjuvant radiotherapy after re-excision also remains as an area of conflict of interest. There may be benefit of adjuvant radiotherapy in patients who have undergone a resection other than a gross total resection. The benefit of adjuvant radiation after gross total excision remains a debatable issue. When planning a patient for re-irradiation the additional toxicity associated must be kept in mind. There is no consensus adjuvant radiation and may have role of radiation and chemo on a case to case basis.

Chemotherapy

In the recent years different chemotherapeutic drugs have been used in patients with recurrent GBM improve disease control.
A wide range of chemotherapy and targeted drugs failed to show any benefit in phase I/II studies and limited phase III studies as well (Table 3). Temozolomide, Bevacizumab, Nitrosoureas are the agents that have shown moderate activity in the treatment of recurrent GBM and further discussion will be on these efficacious regimens only. The patient must be also assessed thoroughly before starting chemotherapy in these patients with special attention to KPS, presence of co-morbidities. The patients who have undergone a surgical excision must undergo an immunohistochemical study for the various predictive factors like MGMT methylation which also help us in tailoring treatment. The chemotherapy may be given alone or after surgery or along with and after radiotherapy in suitable patients.

**Bevacizumab**

Glioblastomas are highly vascularized tumors in which the vascular endothelial growth factor (VEGF) signaling pathway is upregulated. Bevacizumab is a humanized monoclonal antibody against circulating VEGF. Several phase I/II studies reported high responses and improved 6-month progression-free survival with Bevacizumab. Based on these results Bevacizumab, a vascular endothelial growth factor inhibitor received FDA approval for use in recurrent gliomas. Subsequently, a better planned randomized phase 2 BRAIN trial investigated bevacizumab alone and in combination with irinotecan did not show a convincing benefit of Bevacizumab. Based on these results Bevacizumab monotherapy or in combination with Irinotecan was 9.2 months and 8.7 months respectively. Subsequently two metaanalysis established 6-month progress-free survival rates 38–45% and median time to tumor progression 6.1 months. Addition of Irinotecan failed to improve survival.

**Table 2** Summary of the major trials which have used external beam radiotherapy for re-irradiation.

<table>
<thead>
<tr>
<th>Study</th>
<th>Radiation technique</th>
<th>Radiation dose</th>
<th>Concurrent</th>
<th>Survival outcome</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Henke et al. [26]</td>
<td>3d-CRT</td>
<td>20 Gray over 1 week</td>
<td>Nil</td>
<td>Median overall survival 10.2 months</td>
<td>No severe toxicity</td>
</tr>
<tr>
<td>Niyazi et al. [34]</td>
<td>Conventional</td>
<td>36 Gray in 18 fractions</td>
<td>Bevacizumab</td>
<td>Median survival was 311 days</td>
<td>Wound dehiscence –5%</td>
</tr>
<tr>
<td>Cho et al. [28]</td>
<td>SRS vs. FSRT</td>
<td>Median dose 37.5 Gy in 15 fractions -FSRT 17 Gy -SRS</td>
<td>Temozolomide</td>
<td>Median OS 11 months - SRS</td>
<td>Grade III DVT –5%</td>
</tr>
<tr>
<td>Hudes et al. [35]</td>
<td>Hypo fractionated stereotactic radiotherapy</td>
<td>24–35 Gray at 3.0–3.5 Gy per fraction</td>
<td>Nil</td>
<td>Median OS 10.5 months</td>
<td>Late complication rate 23%</td>
</tr>
<tr>
<td>Lederman et al. [36]</td>
<td>Fractionated stereotactic radiotherapy</td>
<td>Four weekly treatments (median dose: 6.0 Gy)</td>
<td>Paclitaxel</td>
<td>Overall median survival was 7.0 months</td>
<td>No grade 3 toxicities</td>
</tr>
<tr>
<td>Grosu et al. [10]</td>
<td>Fractionated stereotactic radiotherapy</td>
<td>Six fractions of 5 Gy</td>
<td>Adjuvant Temozolomide in 60%</td>
<td>Overall median survival was 8.0 months</td>
<td></td>
</tr>
<tr>
<td>Combs et al. [30]</td>
<td>Fractionated stereotactic radiotherapy</td>
<td>Median dose of 36 Gy</td>
<td>Nil</td>
<td>Median overall survival 8 months for patients with GBM</td>
<td>No acute Grade 3/4 neurologic and hematologic toxicity</td>
</tr>
<tr>
<td>Fokas et al. [9]</td>
<td>Hypo fractionated stereotactic radiotherapy</td>
<td>Median total dose of 30 Gy (20–60 Gy)</td>
<td>Nil</td>
<td>Median overall survival was 9.0 months</td>
<td>No higher than grade II toxicity</td>
</tr>
<tr>
<td>Fogh et al. [37]</td>
<td>Hypo fractionated stereotactic radiotherapy</td>
<td>Median dose, 35 Gy in 3.5-Gy fractions</td>
<td>Nil</td>
<td>Median overall survival was 9.0 months</td>
<td>No severe toxicity</td>
</tr>
<tr>
<td>Minniti et al. [38]</td>
<td>Fractionated stereotactic radiotherapy</td>
<td>7.5 Gy delivered in 15 fractions</td>
<td>Temozolomide</td>
<td>Median overall survival was 9.7 months</td>
<td>No severe toxicity</td>
</tr>
<tr>
<td>Van Kampen et al. [39]</td>
<td>Stereotactic radio surgery</td>
<td>17 Gy in one fraction</td>
<td>Nil</td>
<td>Median survival 9 months</td>
<td>No severe toxicity</td>
</tr>
<tr>
<td>Biswas et al. [38]</td>
<td>Stereotactic radio surgery</td>
<td>10–20 Gy in one fraction</td>
<td>Nil</td>
<td>Median survival 6.7 months</td>
<td>No higher than grade II acute side effects</td>
</tr>
<tr>
<td>Patel et al. [41]</td>
<td>SRS or FSRT</td>
<td>FSRT-36 Gy in six fraction</td>
<td>Nil</td>
<td>Median OS 8.5 months - SRS</td>
<td>No severe toxicity</td>
</tr>
</tbody>
</table>
but increased the rate of treatment discontinuation [43,44]. The metaanalysis found no difference in bevacizumab dose–response benefit between 5 mg/kg and 10 to 15 mg/kg. In an interesting revelation Piccioni et al. reported non-inferior outcome with deferred use of bevacizumab in recurrent GBM[45]. In addition discontinuation of Bevacizumab for reason other than tumor progression appears not to adversely affect patient’s outcome[46]. This finding may have an impact in curtailing the cost of care as well. Several phase I/II studies have attempted to combine Bevacizumab with Irinotecan, carboplatin, panobinostat, sorafenib, temsirolimus, Bortezomib, Gefitinib, Erlotinib, Cetuximab, Lenalidomide, Nintedanib, and Veliparib but failed to show improved outcome [47–51].

Nitrosureas

There is also few published literature reporting the efficacy of Nitrosureas in recurrent GBM. These were generally prospective series or phase II studies. Hence the phase II BELOB trial randomly allocated 153 patients with recurrent GBM to treatment with oral lomustine 110 mg/m² once every 6 weeks, intravenous bevacizumab 10 mg/kg once every 2 weeks, or combination treatment with lomustine 110 mg/m² every 6 weeks and bevacizumab 10 mg/kg every 2 weeks [52]. However, lomustine dose was reduced to 90 mg/m² following high rate of grade III/IV thrombocytopenia. The primary endpoint was overall survival at 9 months, analyzed by intention to treat. The trial reported a median survival of 4 months in the combination arm compared to 3 and 1 month in the

### Table 3

**Summarizes different agents used for the treatment of rGBM alone or in combination failed to achieve significant response in phase I/II/III trials.**

<table>
<thead>
<tr>
<th>Drug/Phase</th>
<th>Type of drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verubulin/Phase II</td>
<td>Microtubule destabilizer and Vascular disrupting agent</td>
</tr>
<tr>
<td>Erlotinib + temsirolimus/Phase II</td>
<td>Epidermal growth factor receptor (EGFR) and the mechnistic target of rapamycin (mTOR)</td>
</tr>
<tr>
<td>Sunitinib/Phase II</td>
<td>Inhibitor of several receptor tyrosine kinases</td>
</tr>
<tr>
<td>Fotemustine/Phase I; Phase II</td>
<td>VEGF inhibitor with Nitrosurea</td>
</tr>
<tr>
<td>Enzastaurin/Phase II, Phase III</td>
<td>Selective oral inhibitor of protein kinase Cβ</td>
</tr>
<tr>
<td>Cediranib/Phase III [monotherapy or in combination with Lomustine]</td>
<td>Vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitor</td>
</tr>
<tr>
<td>Dasatinib/Phase II</td>
<td>Multitargeted tyrosine kinase inhibitor</td>
</tr>
<tr>
<td>Bosutinib/Phase II</td>
<td>Kinase inhibitor of Src and Abl</td>
</tr>
<tr>
<td>Cilengitide/Phase II</td>
<td>αv integrin antagonist</td>
</tr>
<tr>
<td>CT-322/Phase II</td>
<td></td>
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<tr>
<td>Veliparib/Phase I</td>
<td>PARP inhibitor</td>
</tr>
<tr>
<td>Pazopanib + Lapatinib/Phase II</td>
<td>Antiangiogenic pazopanib; ErbB inhibitor lapatinib</td>
</tr>
<tr>
<td>Gimatecan/Phase II</td>
<td>Lipophilic oral camptothecin analog</td>
</tr>
<tr>
<td>Nintedanib/Phase II</td>
<td>Triple angiokinase inhibitor</td>
</tr>
<tr>
<td>Vandetanib/Phase II</td>
<td>Multi targeted tyrosine kinase inhibitor</td>
</tr>
<tr>
<td>Patupilone/Phase II</td>
<td>Natural microtubule-stabilizing cytotoxic agent</td>
</tr>
<tr>
<td>Vorinostat/Phase II; Romidepsin/Phase II</td>
<td>Histone deacetylase (HDAC) inhibitor</td>
</tr>
<tr>
<td>T LN-4601/Phase II</td>
<td>Ras-MAPK signaling pathway inhibitor</td>
</tr>
<tr>
<td>Alﬁbercept/Phase II</td>
<td>VEGF Trap</td>
</tr>
<tr>
<td>Sagopilone/Phase II</td>
<td>Lipophylic and synthetic analog of epothilone B</td>
</tr>
<tr>
<td>Rilotumumab/Phase II</td>
<td>A fully human monoclonal antibody against hepatocyte growth factor/scatter factor (HGF/SF)</td>
</tr>
<tr>
<td>Imatinib + hydroxyurea/Phase II</td>
<td>Protein-tyrosine kinase inhibitor that inhibits the BCR-ABL tyrosine kinase</td>
</tr>
<tr>
<td>Didemnin B/Phase II</td>
<td>Natural product derived from the Caribbean Tunic inhibit all phases of the cell cycle</td>
</tr>
<tr>
<td>KRN8602(MX2)/Phase II</td>
<td>Induces rapid and wholesale apoptosis through dual inhibition of PPT1 and EEF1A1</td>
</tr>
<tr>
<td>Thalidomide/Phase II</td>
<td>A novel morpholino anthracycline with capacity to cross BBB</td>
</tr>
<tr>
<td>Paclitaxel/Phase II</td>
<td>Putative inhibitor of angiogenesis</td>
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<tr>
<td>Cystemustine/Phase II</td>
<td>Enhances the polymerization of tubulin to stable microtubules</td>
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<td>Marimastat/Phase II</td>
<td>Nitrosourea</td>
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<tr>
<td>XRS000/Phase II</td>
<td>Matrix metalloproteinase inhibitor</td>
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<td>Gefitinib/Phase II; Erlotinib/Phase II</td>
<td>Tricyclic carboxamide that intercalates DNA and inhibits both topoisomerase I and II</td>
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<td>Cloretazine/Phase II</td>
<td>Epidermal growth factor receptor tyrosine kinase inhibitor</td>
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<td>Cetuximab/Phase II</td>
<td>Novel alkylation agent belonging to 1,2-bis(sulfonyl) hydrazines class</td>
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<td>Trabedersen/Phase II</td>
<td>Anti EGFR monoclonal Antibody</td>
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<td>Bortezomib/Phase II</td>
<td>TGF-β2 inhibitor</td>
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<td>Convection-enhanced delivery (CED) of cintredekin besudotox (CB) was compared with Gliadel wafers (GW)/Phase III</td>
<td>Proteasome inhibitor</td>
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<td>Nitrosourea in Wafer</td>
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Bevacizumab or Lomustine monotherapy arm. 6-month PFS 41%, 16%, 13% and median OS was 11, 8, 8 months respectively in the combination arm and the Bevacizumab or Lomustine monotherapy arm. This trial established an important combination regimen of the Bevacizumab with Lomustine which merits evaluation in phase III study. In addition the survival curves of the two monotherapy arm appear superimposed over each other and there by establish equal effectiveness as monotherapy and may be used in a tailored therapy. Another phase II AVAREG trial randomized patients to receive bevacizumab (BEV) or fotemustine (FTM). The primary end point OS at 6 months was 62% and 73% for bevacizumab and fotemustine, respectively. OS9 (47% and 38%), and median OS (8.7 and 7.2 months) was similar between fotemustine and bevacizumab arms [53]. These findings are not also different to that of the BELOB trial.

Temozolomide

Metronomic Temozolomide has long been considered as an important therapeutic option for recurrent GBM. Different dose schedules 50 mg/m² daily, 120 mg/m² one week on and one week off or 80 mg/m² three weeks on and one week off have been used. In a well-designed phase II RESCUE trial metronomic dose of Temozolomide was used for recurrent glioma. The study revealed significant survival benefit for patients recurring during the course of adjuvant Temozolomide or after longer interval [54]. Grosu et al. in a series of 44 patients administered Temozolomide to 29 patients. Temozolomide was administered one-two cycles before and four to five cycles after re-irradiation [10]. Unlike other studies evaluating chemotherapy, Grosu et al. reported significantly improved survival both in univariate and multivariate analysis. Re-challenge with Temozolomide was further evaluated in a phase II randomized DIRECTOR Trial [55]. Patients with glioblastoma at first progression after Temozolomide/Radiotherapy → Temozolomide and at least two maintenance temozolomide cycles were randomized to one week on (120 mg/m² per day)/one week off or 3 weeks on (80 mg/m² per day)/one week off. Primary endpoint was median time to-treatment failure (TTF). The trial was closed prematurely after 105 patients. Median TTF (1.8 vs. 2 months) and OS (9.8 vs. 10.6 months) were not different between the two arms. The findings support both the regimens of metronomic temozolomide. In addition median TTF was 3.2 months for MGMT methylated tumors compared to 1.8 months in unmethylated tumors. Han et al. evaluated the dose dense temozolomide for recurrent GBM reported modest 10% PFS-6 with median OS of 21.6 weeks [56]. However exploratory analysis revealed median PFS 7.57 weeks in patients with unmethylated MGMT and median OS 19.4 weeks compared to 11.57 weeks and 65.3 weeks for patients with methylated MGMT. This points to an important fact that patients with MGMT methylation are candidates for salvage metronomic temozolomide but MGMT unmethylated patients should be considered for an alternative treatment approach. Attempts to incorporate Irinotecan or other chemotherapeutic agents failed to improve survival [57].

Thus based on current available literature Bevacizumab or Nitrosoureas may be used as single agents in patients with recurrent GBM. Based on the current literature the choice must be based on expected toxicity and cost issues. A combination of Bevacizumab and Nitrosoureas may be used in patients with good performance status and good expected tolerance. Re-challenge with Temozolomide is also a valid option and is of maximum benefit in patients with MGMT methylation. The decision to use chemotherapy thus needs to be personalized regarding the agent, the dose and duration. The chemotherapy may be continued till progression of disease or till when severe toxicity appears.

The patients who undergo surgery may also be considered for adjuvant chemotherapy, with special attention to the various molecular predictive markers in the specimen. The patients with MGMT methylation in the resected specimen may benefit from adjuvant Temozolomide. Bevacizumab must also be used with caution in patients in the immediate post-operative time due to complications of delayed wound healing and lack of evidence of it in the adjuvant setting in re-excised patients. The duration for which the agent must be given is also debatable and there is a lack of any consensus on the same. But if the patient has undergone a biopsy or decompression only chemotherapy may continue till progression.

The addition of Temozolomide with radiotherapy in the re-irradiation setting also merits evaluation. The benefit of concurrent Temozolomide in the primary setting may be extrapolated in the recurrent setting and it is logical to use it in re-irradiation setting also. There are studies reporting the feasibility of concurrent Temozolomide in the concurrent setting, although studies evaluating the specific question are lacking. The adjuvant chemotherapy after re-irradiation may follow the principles of adjuvant chemotherapy after re-excision.

A possible treatment algorithm for recurrent GBM is depicted in Fig. 1.

Novel treatment techniques

NovoTTF is a portable device delivering low-intensity, intermediate frequency electric fields via non-invasive, transducer arrays. The electric fields interfere with cell division by causing misalignment of microtubule subunits in the mitotic spindle during the metaphase to anaphase transition and by dielectrophoretic movement of intracellular macromolecules and organelles during telophase. Kirson et al. reported encouraging 26.1 weeks median time to disease progression and 62.2 weeks median overall survival and paved for a phase III trial [58]. The trial randomized recurrent GBM patients to NovelTTF (20–24 h/day) or chemotherapy of physician’s choice with Primary endpoint of improvement of overall survival. The trial randomly allocated 237 patients to the study and experimental arm. Patient characteristics were well balanced between the two groups. Median survival was 6.6 months in the experimental arm and 6.0 in the chemotherapy arm, progression-free survival rate at 6 months was 21.4% and 15.1% (p = 0.13). Responses were more common in the TTF arm (14% versus 9.6%, p = 0.19). The TTF-related adverse events were mild (14%) to moderate (2%). Severe adverse events occurred in 6% and 16% (p = 0.022) of patients treated with TTF and chemotherapy, respectively. Quality of life analyses was also favorable in the TTF arm [59]. Though the trial did not find a superiority of the TTF over chemotherapy it must be considered an equivalent and less toxic treatment options for these patients. The radiological response which is becoming more a synonym with treatment response for recurrent GBM also favors TTF. Recently a post hoc analysis reported significantly higher OS
in patient’s receiving ≥1 course of NovoTTF Therapy versus BPC (7.7 v 5.9 months). Additional post hoc analysis showed significantly higher median OS with NovoTTF Therapy than with BPC for patients with prior low-grade glioma, tumor size ≥18 cm, Karnofsky performance status ≥80, and those who had previously failed Bevacizumab therapy [60]. These findings are quite encouraging but should be considered hypothesis generating and may be validated in a prospective trial.

Impact of anti-epileptic drugs

In the last decade preclinical studies have suggested that valproic acid (VPA) and its analogs could affect tumor cells in many respects, such as inhibition of a subset of histone deacetylases (HDAC) and cellular kinases, which could affect gene transcription through histone hyper acetylation, DNA hypo-methylation, and modulation of the MAP Kinase signaling pathway [61]. As a result VPA could inhibit tumor angiogenesis and induce differentiation and apoptosis in different types of tumor cells. In addition, clinical studies also have reported prolonged survival in patients with GBM when treated with valproic acid for seizure prophylaxis or treatment [62].

A recently published meta-analysis confirmed the benefit of treatment with VPA (HR, 0.56; 95% CI, 0.44–0.71) [63]. Another recent study evaluated the beneficial role of Levetiracetam in the seizure management or patients with GBM reported encouraging 2.5 months improved PFS for patients receiving LVE for at least a period of three months. This leads researchers to initiate phase II study to evaluate the impact of the anti-epileptic drug (AED) in GBM. In recurrent GBM also the use of AED plays a crucial role and may derive survival benefit [64]. In a recent update Happold et al. conducted a pooled analysis of survival association of AED use at the start of chemoradiotherapy with temozolomide but found no association of PFS and OS advantage for patients taking either VPA or levetiracetam [65]. However, there is much criticism to the pooled analysis as it is also a retrospective study only of many studies which were not intended to answer the question [66].

Similar to AED steroid plays an important role in the management of recurrent GBM also. Dexamethasone is one of the commonly used drugs for these patients to help in reducing symptoms. However, in an exploratory analysis of the NovoTTF trial researchers found a negative impact of using more than 4.1 mg of dexamethasone daily.

Management of recurrent GBM in elderly and pediatric patients

Management of elderly patients with GBM itself is a challenge and is evolving from conventional radiation with concurrent temozolomide to hypofractionated radiation alone or temozolomide alone. However, outcome remains dismal even after any of the treatment approach. However, the management of recurrent GBM poses further challenge as the patients have limited life expectancy and propensity for high rate of complication. Interestingly retrospective data show no increased rate of complication in these patients and median survival for the reoperation group, single-surgery group, and biopsy only group were 18.4, 8.9, and 3.4 months, respectively [67]. Socha et al. analyzed data of 98 elderly frail recurrent GBM patients [68]. Median overall survival from randomization for all patients was 35 weeks and 55 versus 30 weeks for any treatment versus best supportive care (BSC). Median post-progression survival was 15 weeks in the entire cohort and 23 weeks with any treatment versus 9 weeks with BSC. In addition, local treatment (surgery and/or RT) leads to better median PPS of 51 versus 21 weeks for chemotherapy. In patients with poor KPS at relapse median PPS was 9 weeks with BSC versus 21 weeks with any treatment.

Management of newly diagnosed pediatric GBM is another area of concern because of anticipated long term toxicity and concurrent radiation with temozolomide is considered standard [69,70]. However, data are extremely sparse regarding the management of recurrent GBM. However, given the poor
outcomes. Treatment option may follow the approach of adult patients.

Quality of life

Assessment of Quality of Life (QOL) is life and reporting of QOL are areas of unmet need. Presently available therapies are associated with limited survival of less than 12 months. Hence, cost of care and quality of life assessment becomes important for advocating any modality. However, there is limited information on the humanistic burden among patients with recurrent GBM. Only a few studies reported QOL and showed improvement in QOL. Recently Signorovitch et al. conducted a systematic review of Overall Survival, QOL, and Neurocognitive function in rGBM [71]. The authors found very limited data about QOL in rGBM and concluded worse baseline QOL among patients with GMB than among the general population and patients with other cancers. Most importantly the authors reported no improvement in QOL with the presently evaluated treatment options. Bevacizumab alone or in combination also failed to improve QOL [51]. NovoTTF is the only intervention with favorable QOL over chemotherapy in most domains, possibly due to the absence of treatment related toxicities [59].

Future directions

In a pioneering work Verhaak et al. established four different classes of GBM viz., proneural, neural, classical and mesenchymal subtypes with distinct molecular aberration and clinical behavior. The Classical subtype is characterized by Chromosome 7 amplification paired with chromosome 10 loss, and fourfold increase in EGFR expression and lack of p53 mutation. The proneural class shows alterations of PDGFRA and IDH1 mutations. Mesenchymal subtype is characterized by lower NF1 expression, whereas neural subtype shows expression of neuron markers such as NEFL, GABRA1, SYT1 and SLC12A5 [72]. In an interesting revelation Li et al. show a wide difference in the pattern of molecular aberration in primary and recurrent GBM. The authors reported Gene set enrichment analysis revealed that chromatin fracture, repair, and remodeling genes were enriched in recurrent glioblastoma [73]. Majority solid tumors are characterized by increased glucose uptake which may be reflected by elevated glycocalyx even in the presence of oxygen (aerobic glycolysis, the Warburg effect). Preclinical models have shown glioma growth inhibition with reduction in dietary carbohydrates. Feasibility trials are evaluating low-carbohydrate, ketogenic diet containing plant oils for patients with recurrent GBM with encouraging early results [74,75].

In the recent years the efficacy of immunotherapy for cancer has been validated. A wide range of drugs viz. dendritic cell cancer vaccine, Heat-shock protein peptide complex-96 vaccination, humanized monoclonal antibody against the cytotoxic T-lymphocyte antigen-4 (CTLA-4) immune checkpoint, blockade of programmed death 1 (PD-1) and its ligand PD-L1 as well as bioengineered chimeric antigen-receptor T cells has shown appealing response in the treatment of different cancers. Early clinical trials are ongoing with these agents and the results of these trials are eagerly awaited. In the recent studies Schuessler et al. reported possible survival benefit in recurrent GBM when treated with autologous cyto-megalovirus-specific T cells and chemotherapy [76]. These may prove to be beneficial in future trials in recurrent GBM.

Conclusions

Recurrent GBM is a challenge to manage with dismal prognosis. Treatment of rGBM requires a delicate balance between aggressiveness of treatment, outcome, cost of care and quality of life. Surgery, re-irradiation and systemic chemotherapy provide short term disease control and modest survival. Younger patients with preserved performance status should be offered surgery followed by reirradiation or additional salvage chemotherapy, whereas patients with smaller primary in eloquent location and recurrence after long time after primary radiation should be considered for salvage reirradiation along with chemotherapy. MGMT methylation guides to decide between Temozolomide and bevacizumab. Newer targeted therapy, novel treatment technique like NovoTTF, immunotherapy holds promise to impart better survival without compromising on the quality of life.

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Conflict of interest

The authors have no conflict of interest.

Levels of evidence

(I) Evidence from at least one large randomised, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well conducted randomised trials without heterogeneity.

(II) Small randomised trials or large randomised trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity.

(III) Prospective cohort studies.

(IV) Retrospective cohort studies or case–control studies.

(V) Studies without control group, case reports, experts opinions.

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Management of Glioblastoma after recurrence


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