Updates in the Management of Recurrent Glioblastoma Multiforme

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Abstract

Background Glioblastoma is the most aggressive and diffusely infiltrative primary brain tumor. Recurrence is almost universal even after all primary standard treatments. This article aims to review the literature and update the standard treatment strategies for patients with recurrent glioblastoma.

Methods A systematic search was performed with the phrase "recurrent glioblastoma and management" as a search term in PubMed central, Medline, and Embase databases to identify all the articles published on the subject till December 2020. The review included peer-reviewed original articles, clinical trials, review articles, and keywords in title and abstract.

Results Out of 513 articles searched, 73 were included in this review after screening for eligibility. On analyzing the data, most of the studies report a median overall survival (OS) of 5.9 to 11.4 months after re-surgery and 4.7 to 7.6 months without re-surgery. Re-irradiation with stereotactic radiosurgery (SRS) and fractionated stereotactic radiotherapy (FSRT) result in a median OS of 10.2 months (range: 7.0–12 months) and 9.8 months (ranged: 7.5–11.0 months), respectively. Radiation necrosis was found in 16.6% (range: 0–24.4%) after SRS. Chemotherapeutic agents like nitrosourea (carmustine), bevacizumab, and temozolomide (TMZ) rechallenge result in a median OS in the range of 5.1 to 7.5, 6.5 to 9.2, and 5.1–13.0 months and six months progression free survival (PFS-6) in the range of 13 to 17.5%, 25 to 42.6%, and 23 to 58.3%, respectively. Use of epithelial growth factor receptor (EGFR) inhibitors results in a median OS in the range of 2.0 to 3.0 months and PFS-6 in 13%.

Conclusion Although recurrent glioblastoma remains a fatal disease with universal mortality, the literature suggests that a subset of patients may benefit from maximal treatment efforts.

Keywords
- recurrent glioblastoma
- management
- outcomes
- updates

Introduction

Glioblastoma multiforme (GBM) is the most common primary malignant brain tumor in adults. Despite advanced diagnostic modalities and optimal multidisciplinary treatment that typically include maximal surgical resection, radiotherapy (RT) and systemic chemotherapy, tumor treating fields (TTFs), experimental protocols, clinical trials, and best supportive care, most patients experience tumor progression with nearly universal mortality.

Despite multimodality treatments, most clinical trials reported median overall survival (OS) of only 14.6 to 16.7

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months with a 2-year survival rate of 26 to 33%.[1] Recent clinical trial done by Stupp et al[2] reported that addition of TTFs to maintenance temozolomide (TMZ) improved the median OS to 20.9 months as compared with 16.0 months in the TMZ-alone group.

Molecular heterogeneity and inherent or acquired resistance to treatment are the greatest challenges in developing effective treatment for patients with glioblastoma. More than 80% of recurrences are located adjacent to the resection cavity.[3] Uncommon relapse patterns are more common in midline tumors and tumors that infiltrate both hemispheres. To date, several, nonrandomized clinical trials on recurrence are available with heterogeneous patient cohorts, several treatment approaches, and different endpoints recorded. Despite numerous clinical trials, the identification of effective therapies is complex due to the lack of appropriate control arms, selection bias, small sample size, and disease heterogeneity.[4]

Most treatments cannot eradicate all tumor cells, explaining the high rate of recurrence. Surgery is often insufficient, given the diffuse nature of the disease. Re-irradiation may result in local disease control in a proportion of patients, but this approach is not always feasible due to the hazards of cumulative neurotoxicity.[5] Chemotherapy also has major limitations; because most drugs cannot cross the blood–brain barrier, penetration into tumor cells is limited.[4] Therapeutic options need to be carefully weighted, taking into account tumor size and location, previous treatments, age, Karnofsky Performance Score (KPS), patterns of relapse, and prognostic factors.

Since none of the treatments for recurrence is more beneficial than the other, treatment is based on center-specific preferences and patients' individual characteristics. The aim of this review is to evaluate currently applied treatment strategies for patients with recurrent GBM (rGBM) to get more insight into their potential benefit and the optimal approach.

Materials and Methods

The review was designed in accordance to the Preferred Reporting Items for Systematic Reviews and Meta-analyses.

Search Strategy

Articles published in PubMed central, Medline, and Embase databases till December 2020 were all searched. In relevant literature, references were manually searched for additional articles. We screened the title and abstract by combining the term "(recurrent" [All Fields] AND ("glioblastoma" [MeSH Terms] OR "glioblastoma" [All Fields] OR ("glioblastoma" [All Fields] AND "multiforme" [All Fields]) OR "glioblastoma multiforme" [All Fields])) AND (updates [All Fields] AND ("organization and administration" [MeSH Terms] OR ("organization" [All Fields] AND "administration" [All Fields]) OR "organization and administration" [All Fields] OR "management" [All Fields] OR "disease management" [MeSH Terms] OR ("disease" [All Fields] AND "management" [All Fields]) OR "disease management" [All Fields])).

Eligibility Criteria

Only nonexperimental, nonanimal clinical studies were included. Articles written only in English language were considered. We have included only those published articles on rGBM in which patients were managed by surgery and postoperative chemoradiotherapy before recurrence while excluding those articles in which GBMs were managed with either surgery or RT.

Outcomes

Outcomes were measured in median OS (in months), progression-free survival (PFS; in months), and PFS at 6 months (PFS-6; in %). These variables were defined as the median time of intervention to death as median OS and to clinical or radiologic evidence of tumor recurrence/progression as median PFS. PFS-6 was defined as percentage of cases remaining progression free at 6 months from the time of intervention. Clinical deterioration involved worsening/new focal deficits or symptoms of elevated intracranial pressure. Radiologic deterioration involved increased/new tumor contrast enhancement or fluid-attenuated inversion recovery (FLAIR) hyperintensity signal changes, increased mass effect or midline shift, or volume enlargement.

Data Management

Results of the literature search were imported to EndNote X9 (Clarivate Analytics, Philadelphia, Pennsylvania, United States). Software utilization sought to reduce data entry errors and bias (i.e., duplicating references). All investigation reports were reviewed to assess for inconsistencies (e.g., design description, outcome presentation, and total patients analyzed).

Statistical Analysis

Data work was entered in Microsoft office excel 2007 and analyzed using SPSS version 24.0 (IBM Corp.; Chicago, Illinois, United states). Data were analyzed at two levels, descriptive and analytical. Frequency, percentage, range, means, and median were used to describe the characteristics of study participants. A p value < 0.05 was considered statistically significant.

Results

In all, 513 articles were identified on searching the PubMed central, Medline, and Embase databases. Out of the 513 articles, 183 articles were screened based on removal of duplicates. After screening for eligibility of potential articles, 73 studies were included in this review (►**Fig. 1**).

On analyzing the literature, most of the studies report a median survival in the range of 5.9 to 11.4 months after re-surgery and 4.7 to 7.6 months without re-surgery (►**Table 1**). The predicting factors for improved outcomes in these studies were (1) age <60 years, (2) good performance status of the patients (KPS ≥70, (3) extent of resection (EOR) at re-surgery, (4) gross total resection (GTR) at initial surgery, and (5) adjuvant therapy after initial surgery.

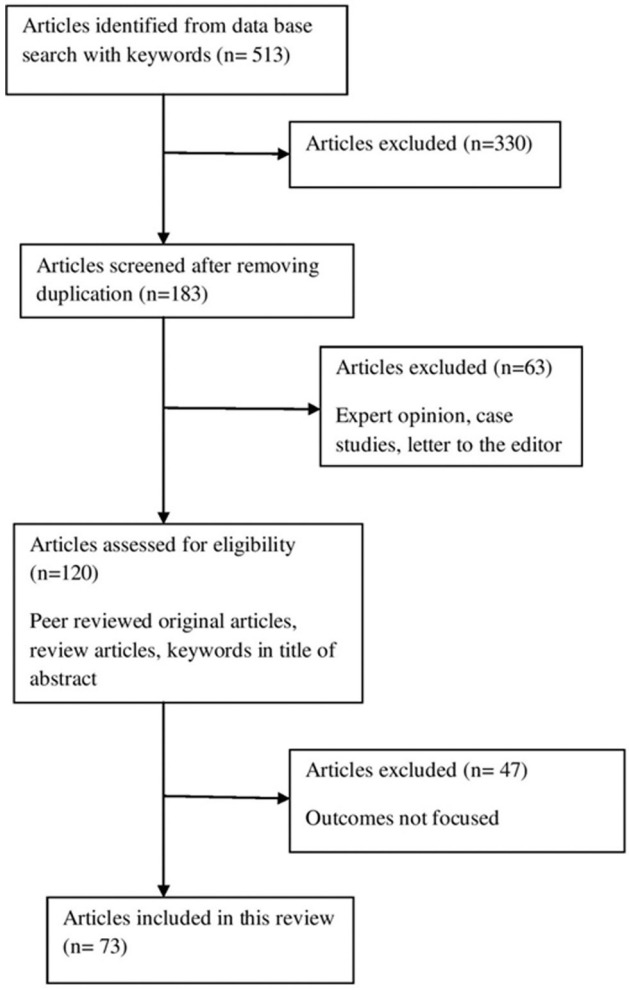

Fig. 1 Flowchart (Preferred Reporting Items for Systematic review and Meta-Analysis) for article selection.

On reviewing the published literature, re-irradiation with stereotactic radiosurgery (SRS) at a dose of 13 to 18 Gy results in a median OS of 10.2 months (range: 7–12 months) and 16.6% (range: 0–24.4%) radiation necrosis (►**Table 2**). The re-irradiation with fractionated stereotactic radiotherapy (FSRT) with a median dose of 36 Gy (range: 22–55 Gy) delivered at a median time interval of 11.6 months (range: 3.5–19months) resulted in a median OS of 9.8 months (range: 7.5–11 months). The re-irradiation toxicity and factors associated with improved outcome are given in ►**Table 2**.

On evaluating previous studies, chemotherapy with carmustine had PFS-6 of 13-17.5% and median OS of 5.1 to 7.5 months, chemotherapy with lomustine had PFS-6 of 19 to 24.5% and median OS of 7.1 to 9.8 months, and fotemustine had PFS-6 of 20.9 to 61% and median OS of 6.0 to 11.1 months (►**Table 3**). Bevacizumab (BEV) resulted in a median PFS-6 of 25 to 42.6%, a median OS of 6.5 to 9.2 months, and a radiologic response of 25 to 57% (►**Table 3**). Other anti-angiogenic agents including cediranib and aflibercept had been evaluated in the treatment of rGBM, and allowed to achieve a PFS-6 of 25.8 and 7.7%, respectively. TMZ rechallenge was evaluated in six studies in patients with rGBM pretreated with TMZ, by applying different metronomic schedules. Overall PFS-6 was 23 to 58.3% and median OS was 5.1 to 13.0 months, respectively (►**Table 3**).

In most trials in which the rGBM patients were treated with epithelial growth factor receptor (EGFR) inhibitors (erlotinib/gefitinib), the results were disappointing (PFS of 2–3 months for erlotinib and PFS-6 of 13% for gefitinib; ►**Table 4**). Different combination schedules of these chemotherapeutic drugs and there toxicity are given in ►**Table 4**.

Discussion

Glioblastoma is the most common malignant primary brain tumor. Overall, the prognosis for patients with this disease is poor, with a median survival of less than 2 years. Recurrence occurs in spite of standard treatment. Despite recent advances in the understanding of the molecular heterogeneity, tumor phenotype, and tumor microenvironment that provide insight into potential targets for targeted therapies, the treatment of recurrent glioblastoma is challenging. At recurrence, there are limited options, and this includes re-surgery, re-irradiation, systemic chemotherapy, immunotherapy, molecular-targeted therapy, TTFs, and best supportive care.

Re-surgery

Re-surgery should be considered a therapeutic strategy in selected patients of rGBM. When feasible, surgical resection is associated with improved OS. The decision for re-surgery after recurrence should be individualized as it is associated with greater morbidity and mortality. The goal of re-surgery should be to relieve the mass effect and to achieve safe maximal EOR, which improves survival and also the overall effect of adjuvant therapy. It can also help establish further molecular markers for novel adjuvant therapies, immunotherapies, and prognostications.[74] Surgery should be considered under the following: (1) when the procedure can reduce the raised intracranial pressure; (2) when the patient is in better functional status; (3) when it can reasonably improve the quality of life of the patient; (4) when it did not cause significant new neurologic deficit or morbidity, precluding further adjuvant therapies; (5) when it is possible to resect the contrast-enhancing tumor tissue[75]; and (6) when the disease is focal and not involving eloquent brain regions, deep structures, or both hemispheres. Intraoperative neurophysiologic monitoring (IONM) and awake craniotomy help maximize the EOR of rGBM located in eloquent areas of the brain and minimize the postoperative deficits.[76]

On reviewing the literature, we found that most of the previous studies demonstrated the benefits of re-surgery in recurrent setting but some differed. Study done by Franceschi et al showed no significant benefits of re-surgery, with age ($p = 0.001$), O^6-methylguanine-DNA methyltransferase (MGMT) methylation ($p = 0.002$), and PFS-6 ($p = 0.0001$) being the significant prognostic factors on multivariate analysis.[12] Ringel et al[75] compared the survival outcome after resection with major trials on second-line chemotherapy. The median OS was found to be superior after re-surgery (11.9 months) as compared with the second-line

Table 1 Previous studies showing median survival after re-surgery and factors predicting improved outcomes

Study	No. of patients	Median survival after re-surgery in months (vs. no re-surgery)	Median survival from diagnosis in months (vs. no re-surgery)	Factors predicting improved outcomes
Helseth et al[6]	65	5.9	18.9 (vs. 8.6)	Age <60, ECOG 0–2, surgery vs. biopsy, unilateral vs. bilateral
Tugcu et al[7]	50	6.1	9.6 (vs. 6.7)	Younger age, male gender, higher KPS at discharge, GTR, reoperation, and radiotherapy
Rusthoven et al[8]	51	9.0 (vs. 4.9)	22.2 (vs. 14.2)	Age <50, WHO grade III, interval between operation 6 mo
Clark et al[9]	174	9.75	21.8	NR
Park et al[10]	55	10	13	KPS ≥ 70, ependymal involvement
McNamara et al[11]	584	7	20.9 (vs. 9.9)	Neutrophil/lymphocyte ratio ≤4
Franceschi et al[12]	232	9.6 (vs. 7.6)	25.8 (vs. 18.6)	Age, MGMT methylation, PFS at 6 mo
Brandes et al[13]	270	11.4	27.6	Age <50, MGMT methylation, GTR
Chen et al[14]	65	13.5 (vs. 5.8)	25.4 (vs. 11.6)	Age at first presentation, KPS at recurrence, GTR (EOR), re-surgery
Delgado Fernandez et al[15]	121	16.4 (vs. 10.5)	24.2 (vs. 8.4)	Age <60, KPS >80, GTR at initial surgery, adjuvant therapy after initial surgery
Zanello et al[16]	777	8	19	KPS <70, TMZ, bevacizumab
Wann et al[17]	120	9.6 (vs. 4.7)	22 (vs. 14)	Re-surgery, chemotherapy

Abbreviations: ECOG, Eastern Cooperative Oncology Group performance status; EOR, extent of resection; GTR, gross total resection; KPS, Karnofsky Performance Score; MGMT, methyl guanine methyl transferase; NR, not recorded; OS, overall survival; TMZ, temozolomide.

Table 2 Previous studies showing median survival outcome after re-irradiation

Study	No. of cases	Mode of RT	Median dose	Median OS (in mo)	Toxicity
Kohshi et al[18]	11	CFRT	22 Gy in 8 Fr	11	No
Combs et al[19]	325	CFRT	36 Gy in 20 Fr	7.5	NR
Fokas et al[20]	53	CFRT	30 Gy in 10 Fr	9.0	No
Combs et al[21]	172	FSRT	36 Gy, 5 × 2 Gy/wk	8.0	RN in 1 case
Laing et al[22]	22	FSRT	55 Gy in 6–10 Fr	9.8	RN in 5 case
Hudes et al[23]	25	FSRT	24 Gy in 3 Fr	10.5	No grade 3 toxicity
Fogh et al[24]		FSRT	35 Gy in 3.5 Fr	11.0	NR
Kong et al[25]	114	SRS	16 Gy, MTV 10.6 cm^3	23 (vs. 12)	RN in 24.4%
Shrieve et al[26]	86	SRS	13 Gy, MTV 10.1 cm^3	10.2	No
Comb et al.[27]	32	SRS	15 Gy	10.0	No
Pinzi et al[28]	42	SRS	15 Gy	11.5	RN in 6%
Patel et al[5]	26	SRS	18 Gy	8.4	RN in 3.8% cases
Park et al[29]	11	SRS + BEV	16 Gy, GTV 13.6 cm^3	18 (vs. 12)	Grade 3 toxicity in 1 case
Cuneo et al[30]	63	SRS + BEV	18 Gy	11.2	12.7% had grade 3/4 toxicity, RN in 10%
Flieger et al[31]	57	FSRT + BEV	36 Gy in 12 Fr	8.6 (vs. 5.7)	7% had ≥grade 3 toxicity
Niyazi et al[32]	30	FSRT + BEV	36 Gy in 18 Fr	PFS-6, 72 vs. 24%	RN in 2 cases
Conti et al[33]	23	SRS + TMZ	20 Gy in 2 Fr	12.0 vs. 7.0	Corticosteroid dependency in 63%

Abbreviations: BEV, bevacizumab; CFRT, conventional fractionated radiotherapy; Fr, fraction; FSRT, fractionated stereotactic radiotherapy; Gr, gray; GTV, gross total volume; MTV, median tumor volume; NR, not recorded; OS, overall survival; PFS-6, progression-free survival at 6 months; RN, radian necrosis; RT, radiotherapy; SRS, stereotactic radiosurgery; TMZ, temozolomide.

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Table 3 Previous studies on role of chemotherapy in rGBM

Chemotherapeutic agent	Study type	No. of patients	PFS-6	Median OS (in mo)	Toxicity	Studies
BCNU (carmustine)	2 phase II and 1 retrospective	69 & 35	13–17.5%	5.1–7.5	Hematologic, hepatic and pulmonary	Brandes et al,[34] van den Bent et al,[35] and Reithmeier et al[36]
Lomustine	2 phase III	92 + 325	19–24.5%	7.1–9.8	Hematologic: 30 and 7 cases; Nonhematologic: 16 and 6 cases	Ahluwalia[37] and Batchelor et al[38]
Fotemustine	prospective phase II trial	160	20.9–61%	6–11	Hematologic toxicity (grades 3 and 4)	Scoccianti et al,[39] Brandes et al,[40] Fabrini et al,[41] and Addeo et al[42]
Procarbazine+ lomustine+ vincristine	2 retrospective	149	29–38.4%	7.7–7.8	26% hematologic toxicity (grade 3–4)	Kappelle et al[43] and Schmidt et al[44]
TMZ rechallenge	6 phase II	239	23–58.3%	5.1–13	Hematologic toxicity (grades 3 and 4)	Franceschi et al,[45] Kong et al,[46] Berrocal et al,[47] Perry et al,[48] Kong et al,[49] and Hammond et al[50]
TMZ	RESCUE trial	91	23.9%	9.3	NA	Perry et al[48]
TMZ (daily low dose) + Sorafenib	Phase II	32	9.4%	NA	Hematologic: 14 Nonhematologic: 12	Yung et al[51]
TMZ (continuous low dose) + celecoxib	Retrospective	28	43%	16.8	lymphopenia	Stockhammer et al[52]
TMZ+ O^6 benzyl guanine	Phase II	34	9%	4.5	NA	Quinn et al[53]
Bevacizumab	3 phase II and 1 retrospective	183 and 50	25–42.6%	6.5–9.2	HTN, thromboembolism, fatigue	Friedman et al,[54] Kreisl et al,[55] Raizer et al,[56] and Chamberlain and Johnston[57]
Bevacizumab + irinotecan	Meta-analysis		30–50.3%	6.1–9.7	HTN, thromboembolism	Zhang et al[58]
Bevacizumab + irinotecan + cetuximab	Phase II	43	33%	7.0	Skin toxicity	Hasselbalch et al[59]
Bevacizumab + carboplatin + etoposide	Phase II	6	22%	6.9	Hematologic: 2; Nonhematologic: NA	Francesconi et al[60]
Bevacizumab + etoposide	Phase II	27	44.4%	10.2	Hematologic: 5; Nonhematologic: 2	Reardon et al[61]
Bevacizumab + erlotinib	Phase II	24	29%	10.3	Hematologic: 4	Sathornsumetee et al[62]
BELOB Bevacizumab and lomustine alone and in combination	RCT	148	18% 13% 42%	8.0 8.0 12.0	HTN and fatigue: 2 patients in bevacizumab arm and 5 patients in combination arm	Taal et al[63]
Average study Bevacizumab or fotemustine	Phase II	59 21	62.1% 73.3%	7.3 8.7	NA	Brandes et al[64]
Aflibercept	Phase II	42	7.7%	9.1	Asthenia, HTN	de Groot et al[65]
Cediranib	Phase II	31	25.8%	9.4	Hematologic: 7	Batchelor et al[66]

Abbreviations: HTN, hypertension; NA, not available; OS, overall survival; PFS 6, progression-free survival at 6 months; RCT, randomized control trial; TMZ, temozolomide.

Table 4 Molecular-targeted therapy in rGBM

Molecular agent	Study type	No. of patients	PFS-6	Studies
Erlotinib	Phase II	48	PFS 3.0 m	Yung et al[67]
Erlotinib	Phase I/II	53	PFS 2.0 m PFS-6: 11.4%	Raizer et al[68]
Gefitinib	Phase II	53	13%	Quant et al[69]
Everolimus + gefitinib	Pilot study	19	PFS 2.6 m	Nguyen et al[70]
Erlotinib/gefitinib + sirolimus	Pilot study	28	25%	Doherty et al[71]
Erlotinib + carboplatin	Phase II	43	14%	de Groot et al[72]
EORTC trial Erlotinib vs. TMZ or carmustine	Phase II	56 54	12% 24%	Soffietti et al[73]

Abbreviations: EORTC, European Organisation for Research and Treatment of Cancer; PFS-2.0, progression-free survival at 2.0 months; PFS-2.6, progression-free survival at 2.6 months; PFS-3.0, progression-free survival at 3.0 months; PFS-6, progression-free survival at 6 months; rGBM, recurrent glioblastoma multiforme; TMZ, temozolomide.

chemotherapy (4.5–10.8 months).[75] The oncologic benefits of re-surgery need to be balanced against the complication rates of re-surgery. A recent publication on surgical outcome in rGBM reported overall complication rates of 12.8, 27, 22, and 22.2% and neurologic complication rates of 4.8, 12.1, 8.2, and 11.1% after the first, second, third or fourth, and more than four surgeries, respectively.[77]

Controversy also exists in the EOR at re-surgery. Most of the previous studies observed that EOR at re-surgery had improved outcomes (►**Table 1**). Involvement of eloquent brain usually precludes this objective and is associated with shorter OS.[78] On the contrary, survival analysis in other studies showed no significant differences between patients receiving gross total (11 patients) or partial (22 patients) tumor resection (Breslow's test, $p = 0.20$; log-rank test, $p = 0.27$; respective median OS at 10 months [95% confidence interval (95%CI): 1–20] and 9 months [95%CI: 4–14]).[79] The DIRECTOR trial (Comparison of Two Dosing Regimens of Temozolomide in Patients with Progressive or Recurrent GBM; ClinicalTrials.gov identifier NCT00941460) allowed the retrospective analysis of EOR and residual tumor volume in approximately two-thirds of the patients, who underwent surgery prior to study entry. Complete resection of enhancing tumor was achieved in 68% of patients and in multivariate analysis it was found to be an independent predictor of postresection survival (12.9 months [CI 95%: 11.5–18.2] in complete resection group versus 6.5 months [CI 95%: 3.6–9.9], $p = 0.001$).[80]

One of the other benefits of re-surgery is it can allow for placement of intralesional chemotherapy with carmustine wafers (Gliadel). A phase III study including 222 patients had compared re-surgery plus carmustine wafers ($n = 110$) versus re-surgery alone ($n = 112$). The median OS was improved in the carmustine wafers group (31 vs. 23 weeks; $p = 0.006$).[81] In another study, 22 patients received carmustine wafers at first progression of GBM. The median OS was 9.9 months and PFS-6 was 27.2%.[82] The most common complication was postoperative infection. Other adverse events included edema-related intracranial pressure changes, delayed wound healing, epileptic seizure, and neurologic worsening.[83]

Re-irradiation

Re-irradiation is another option to be considered as a salvage therapy in rGBM. Re-irradiation is generally controversial because of the risk of toxicity. In fact, the high RT dose typically applied in first-line treatment to reduce the risk of in-field relapse (~60 Gy) generally hampers use of a second full-dose RT course. However, re-irradiation has been shown to be of value after local relapse. Newer treatment techniques enable delivery of radiation more precisely to the target without crossing the tolerance of normal surrounding structures.[84]

SRS has the ability to deliver a single high dose of radiation to a tumor with the capacity to spare surrounding normal tissue due to very steep dose gradient generated by conformal treatment.[85] On evaluating the published literature, after re-irradiation with SRS doses of 13 to 18 Gy in rGBM, the median OS was 10.2 months (range: 7–12 months) and radiation necrosis was 16.6% (range: 0–24.4%; ►**Table 2**). Thus, use of SRS improved survival in rGBM with small volume as compared with the historical control group with a moderate risk of radiation necrosis.[25–28]

FSRT offers the ability to reduce treatment margins and volume with more conformal treatment compared with even primary treatment and allow for higher dose per fraction treatment. There is less concern for potential severe side effect than may be with SRS alone. On analyzing the literature, with re-irradiation with FSRT with a median dose of 36 Gy (range: 22–55 Gy) delivered at a median time interval of 11.6 months (range: 3.5–19months), the median OS was 9.8 months (range: 7.5–11 months). The survival gain was almost the same as that from a single-fraction SRS with reduce risk of radiation necrosis (1/172 in Combs et al[21] and 5/22 in Laing et al[22]), which were easily controlled with steroid.[86] Better survival was noted with KPS >70%, age <50 years, radiation dose >30 to 36 Gy, target volume <20 to 30 mL, and time interval >12 months between the first RT and re-radiotherapy by multivariate analysis.[2] Thus, fractionated re-irradiation was safe and it could give moderate survival prolongation with reduced risk of radiation necrosis to selected cases of rGBM. By conventional fractionated re-

irradiation with median cumulative equivalent dose of 99.3Gy at the rate of 2 Gy/fraction, symptomatic persistent brain stem or optic apparatus injury was not observed at the median cumulative brain stem dose of 76.9 Gy (5.0–108.3 Gy) and optic apparatus doses of 56.6 Gy (4.5–90.9 Gy).[87] Analysis of previous data demonstrated that re-irradiation yielded clinical improvement in 24 to 45% of patients and reduction in steroid dependency in 20 to 60% of patients.[86]

Retrospective analysis of re-irradiation for rGBM has suggested that median OS (~9.8 months) does not differ significantly among conventional fractionated radiotherapy (CFRT), FSRT, and SRS, but has a significantly lower risk of radiation necrosis in CFRT and FSRT as compared with SRS.[88] Although standards of re irradiation are not yet defined for rGBM mainly due to paucity of high-level prospective or randomized control studies, re-irradiation of various techniques is an established salvage option for selected patients.

Cumulative radiation dose of the two courses of irradiation is calculated as biological-equivalent total dose normalized to 2 Gy/fraction (Eq. D2). The median cumulative Eq. D2 reported in conventionally fractionated re-irradiation (81.6–101.9 Gy) series was generally lower than those observed in hypofractionated SRT (90–133.9 Gy) and SRS (111.6–137.2 Gy). The estimated risk of radiation necrosis at 1 year was 0, 2 to 12, and up to 17% for cumulative Eq. D2 <96, >96.2, and >137 Gy, respectively.[89] The time interval between two radiation courses was not associated with increased risk of radiation necrosis.[89]

Chemotherapy

Chemotherapy is another treatment option in selected rGBM patients. Nitrosourea compounds are alkylating agents characterized by high lipophilicity, allowing them to cross the blood–brain barrier. Vincristine is a relatively large (molecular weight of ~825 Da), lipid-soluble plain alkaloid. Large size leads to lack of penetration into the normal brain. On intra-arterial administration, the brain tumor penetration of vincristine is also low. The arrival of TMZ has diminished the use of vincristine (also of the procarbazine, lomustine, and vincristine [PCV] regime) based on low blood–brain barrier transport and disparate clinical trials result.[90]

Lomustine is a lipid-soluble, alkylating agent. It permeates the blood–brain barrier well, which a priori makes it a reasonable candidate for chemotherapy of intrinsic brain tumors. It probably remains the most widely used drug second only to TMZ in the treatment of glioma. It is defined as the main standard of care for rGBM in Europe where BEV is not approved by the European Association for Neuro-Oncology (EANO),[91] and has been frequently administered in clinical trials as the common comparator for other antitumor drugs.[92]

Nitrosourea compounds were evaluated in various phase I/II trials in patients with rGBM pretreated with TMZ. On analyzing these trials, the nitrosourea compounds seem comparable in terms of efficacy at clinically tolerated doses, whereas nonhematologic toxicity, notably lung fibrosis, may be more common with carmustine than others.[34–42] Two retrospective studies evaluated the combination of PCV in rGBM patients. Similar efficacy findings were reported in those two studies: PFS-6 of 30 to 38% and OS of 7.6 to 7.9 months with 26% of the patients having grade 3/4 hematologic toxicity.[43,44] Significant hematologic toxicity concern and availability of more effective agents have made the use of nitrosourea less desirable.

Antiangiogenics

BEV is a monoclonal antibody with activity against vascular endothelial growth factor (VEGF). Different retrospective and prospective studies have evaluated the treatment effect of BEV as monotherapy or on combination with other agents including irinotecan, etoposide, TMZ, carboplatin, cetuximab, and erlotinib in rGBM. To date, none of these agents have proved more effective than BEV only.[58–62] The various studies demonstrated median PFS-6 of 25 to 42.6%, median OS of 6.5 to 9.2 months, and radiologic response of 25 to 57%.[73] There was no significant difference in OS or PFS between the groups treated with BEV 5 versus 10 mg/kg. There were more adverse events seen in patients treated with BEV 10 mg/kg.[93]

Other antiangiogenic agents including cediranib and aflibercept have been evaluated in the treatment of rGBM, and their PFS-6 was 25.8 and 7.7%, respectively.[65,66] None of these agents achieved an effectiveness that improved upon BEV.

Temozolomide Rechallenge

TMZ rechallenge was evaluated in six studies in patients with rGBM pretreated with TMZ. Different metronomic schedules were employed, including 40 to 100 mg/m^2 daily doses given for 21 to 365 consecutive days as well as alternating 1 week on/1 week off regimens. Overall PFS-6 and median OS were 23 to 58.3% and 5.1 to 13.0 months, respectively.[45–50]

The DIRECTOR trial compared 1 week on (120 mg/m^2/d)/1 week off versus 3 weeks on (80 mg/m^2/d)/1 week off TMZ regimens in patients after first recurrence and after at least two cycles of TMZ. It is supposed to show a superiority of the 1 week on/1 week off versus 3 weeks on/1 week off regiment over the metronomic TMZ schedule.[94]

RESCUE phase II trial[48] evaluated the best timing of TMZ rechallenge by prospectively dividing the 91 rGBM patients into three groups according to TMZ free interval. The trial concluded that the most significant benefit was shown in patients who had completed a previous course of concomitant TMZ/RT with adjuvant TMZ followed by a treatment-free interval of at least 2 months (PFS-6 of 35.7%). The patients who progressed while still on adjuvant TMZ therapy beyond six cycles did significantly worse (PFS-6: 7.4%), but those who progressed before completion of adjuvant TMZ had a better response (PFS-6: 27.3%). The investigators hypothesized that a continuous regimen might lead to a depletion of MGMT and restoration of TMZ sensitivity as had been previously reported.[51]

Various studies had evaluated the response of TMZ in combination with other chemotherapeutic drugs in rGBM patients. TMZ had given with sorafenib, celecoxib, and O^6-benzylguanine and had reported PFS-6 of 9.4, 43, and 9%,

respectively.[51–53] Overall, the TMZ combination studies available to date do not suggest that one particular chemotherapy combination is more effective than TMZ alone.

Molecular-Targeted Therapy

EGFR amplification and overexpression present in ~50% of GBM patients and are associated with poor prognosis. Treatment against specific molecular targets, in particular the EGFR, has been investigated in rGBM patients. In most trials, the rGBM patients have been treated with EGFR inhibitors (erlotinib/gefitinib); the results were disappointing (PFS of 2–3months for erlotinib and PFS-6 of 13% for gefitinib).[67–69] Gefitinib was given with everolimus in a phase I/II trial but PFS (2.6 months) was similar to that achieved with monotherapy.[70] Sirolimus was added with erlotinib in a pilot study and with carboplatin in a phase II trial in rGBM patients and showed a PFS-6 of 25 and 14%, respectively.[71,72] The European Organisation for research and treatment of Cancer (EORTC) trial compared the efficacy of erlotinib with TMZ or carmustine in 110 rGBM patients. The PFS-6 was 12% in patients treated with erlotinib and 24% in patients receiving either TMZ or carmustine.[35] The investigators concluded that the response to erlotinib did not correlate with EGFR or EGFRVIII.

INTELLANCE II study was a randomized multicentric study that analyzed the efficacy of Depatux-M alone versus Depatux-M plus TMZ versus the standard treatment of lomustine or TMZ in EGFR amplified GBM patients relapsing after the Stupp protocol.[95] The primary analysis with a median follow-up of 14.4 months showed a trend of longer survival for the combination regimen versus the standard treatment. The 12-month OS rate was 39.7 versus 28.2%, respectively, with p value of 0.06 (hazard ratio [HR] = 0.71; 95% CI: 0.50–1.02). In the subsequent long-term analysis with a median follow-up of 28.7 months, the OS difference between the two arms was statistically significant. The 2-year survival in the combination arm was 19.8 versus 5.2% in the control arm ($p = 0.017$; HR = 0.66; 95% CI: 0.47–0.93). High rate of high-grade ocular toxicity further reduces the quality of life in recurrent situation. The most frequent adverse events in patients treated with Depatux-M were ocular and were observed in 81% of patients (any grade). In most cases, the ocular events occurred after the second administration of Depatux-M. Ocular adverse events were attributed to microcystic keratopathy and included keratitis (67%), photophobia (8%), eye pain (3%), and conjunctivitis (3%). Grade 3 keratitis was reported in 11% cases and no grade 4 adverse events were recorded. The ocular toxicity caused by Depatux-M was reversible, if managed carefully.[96,97] This trial suggests a role for the use of Depatux-M in combination with TMZ in EGFR-amplified recurrent glioblastoma, but its findings are not supported by the companion phase III study in newly diagnosed glioblastoma. The efficacy in glioblastoma of other antibody drug conjugates (ADCs) targeting the EGFR but with a better safety profile should be explored.

Check point inhibition: Nivolumab is a human immunoglobulin G4 monoclonal antibody targeting the programmed death-1 (PD-1) immune checkpoint receptor. The checkmate 143 randomized clinical trial was the first phase III study investigating the use of PD-1 inhibitor in patients with rGBM. The trial had compared the use of nivolumab and nivolumab plus ipilimumab in patients with rGBM. The median OS with nivolumab was 10.4 months, and with combination arm was 9.2 months, appears to be consistent with those historically observed with other therapies in rGBM.[98] A randomized phase III cohort 2 of checkmate 143 had compared nivolumab monotherapy with BEV monotherapy in rGBM patients. The study did not meet the superior OS with nivolumab. At median follow-up of 9.5 months, the median OS was compared between the groups: nivolumab, 9.8 months (95% CI: 8.2–11.8); BEV, 10.0 months (95% CI: 9.0–11.8); HR, 1.04 (95% CI: 0.83–1.30), with $p = 0.76$.[99] The PFS and objective response rate (ORR) were numerically better in the BEV group. The duration of response was numerically longer in the nivolumab group. The toxic effect was consistent with the known safety profiles of nivolumab and BEV.[54,100] MGMT promoter methylation and baseline use of corticosteroid were known prognostic factors for patients with rGBM. Their role in survival was also evaluated in subgroup analysis.[101,102] The post hoc subgroup analysis indicated that the subgroup of patients with rGBM with methylated MGMT promoter and no baseline corticosteroid dependence may be most likely to derive benefit from immune checkpoint inhibition.[99] Checkmate 143 trial still favored the BEV group even if tumor PD-L1 expression >1% (the classified level of positive PD-L1 expression are ≥1% , ≥5%, and ≥10% of tumor cells),[103] as it has been shown to increase PFS and ORR numerically better than nivolumab group, improve peritumoral edema, and reducing the need for immunosuppressive glucocorticoids known to interfere with efficacy of immunotherapy. So a positive biomarker did not influence clinical outcome.[104]

REGOMA trial (a randomized phase II trial) compared regorafenib (oral multikinase inhibitor) with standard lomustine in rGBM patients. They found a 12-month improvement in OS in patients treated with regorafenib (38.9 vs. 15.0%).[99] Due to this important clinical benefit, regorafenib was included in the National Comprehensive Cancer Network (NCCN) 2020 guidelines and was approved by the Italian Medicines Agency (AIFA) as the preferred treatment for the rGBM population.[105]

Immunotherapy

Dendritic cell vaccination (DCV): It is an active immunotherapy that aims at inducing an antitumor immune response. Patients are vaccinated with tumor-associated antigen (TAA) loaded DC with the concept that they migrate to the local lymph nodes, present TAA-derived peptide on human leukocyte antigen (HLA) molecule, and initiate antitumor T-cell response, which selectively kills the tumor cells and prevents tumor recurrence due to immunologic memory.[99] Yao et al[106] did a randomized phase II trial on 41 newly diagnosed and rGBM patients, and reported that DCV significantly prolongs the median OS (13.7 vs. 10.7 months). Even after more than 10 years of DCV in GBM and rGBM patients, it is still difficult to draw conclusion as to the efficacy of DCV.

Viral injection therapy: It is a special type of immunotherapy, administered intravenously or in situ (peritumorally after resection of the rGBM or intratumorally via a stereotactic-guided catheter or via convection-enhanced delivery). Two types of viral vectors are utilized: the first uses viral vectors that infect and do not replicate but still deliver an anticancer gene, while the second uses replication competent viruses that infect and replicate. The first (gene therapy) has found several Food and Drug Administration (FDA) approved applications for noncancer human disease, while the second has been exclusively used for cancers. A phase I clinical trial, stereotactic injection of an engineered herpes simplex virus I (HSV I; G 207) in rGBM patients showed an average survival of 12.8 months.[107] Phase III randomized controlled trials (RCTs) are required to determine the effectiveness of virotherapy in rGBM.

Tumor Treating Fields

Two clinical trials have assessed the effect of alternating electric field (AEF) using the Novo TTF-100A device in rGBM patients. In the first trial, a small pilot study of 10 patients, the median OS was 62.2 weeks (vs. 29.3 weeks in the control arm) and PFS-6 rate was 50% (vs. 15.3% in the control arm). Patients had well tolerated the TTF except dermatitis beneath the electrodes.[108,109] Another phase III randomized multicentric clinical trial was designed to compare the safety and effectiveness of Novo TTF-100A with the best standard of care (BSC) in 237 rGBM patients (120 TTF and 117 BSC). Although, there was no significant difference between TTF and BSC groups in the OS (6.0 vs. 6.6 months, $p = 0.27$), PFS-6 (21.4 vs. 15.1%, $p = 0.13$) and response rates (14 vs. 9.6%, $p = 0.19$), but the OS and 1-year survival rate appeared higher in the TTF group patients, which were treated as per protocol than those who did not receive the complete therapy. There were no statistical analyses provided to determine whether this difference was significant, notwithstanding the fact that the trial was never designed as a noninferiority trial and therefore was unable based on power analysis to determine equivalence with BSC. The NovoTTF-100A device was approved by the FDA in April 2011 for the treatment of adult patients with recurrent GB after receiving upfront standard of care.[110]

Photodynamic therapy (PDT): It involves photoactivation of a photosensitizer molecule that is selectively incorporated into neoplastic cells. Photoirradiation activates the photosensitizer by transfer of energy to the sensitizer resulting in excitation of molecular oxygen to a singlet (energy is converted to heat or is emitted as light) or a triplet state. In the triplet state, the energy generates reactive oxygen species (ROS) necessary to induce cell death. Review of the available literature suggests that PDT can be safely delivered to prevent local tumor recurrence. However, lack of clear efficacy of PDT in OS has limited the widespread adoption of this technology and implementation as a treatment of rGBM.[111] A multicentric, randomized, nonblind trial (NOA-11 trial, ClinicalTrial.gov Identifier: NCT04469699) is underway to evaluate the safety and efficacy of stereotactic PDT with 5-aminolevulinic acid in rGBM patients.

Intraoperative radiotherapy (IORT): It is the application of low-energy photons immediately after surgery and restricted to the surgical margin. In a recent phase I/II trial, this novel approach of local dose escalation yielded a median PFS of 11.2 months and a median local PFS of 14.3 months, with isolated distant recurrence as the predominant pattern of failure.[112] Further RCTs are required to evaluate the efficacy of IORT.

Laser interstitial thermal therapy (LITT): It is a minimally invasive therapy and is performed under imaging and stereotactic guidance to precisely direct the probe and ablate the area of interest using real-time magnetic resonance thermography. LITT also offers the ability to treat recurrent tumor in deep or eloquent area that would be considered inoperable for open surgery.[113] Schwarzmaier et al reported 16 patients with rGBM treated with LITT and a median OS of 11.6 months.[114] Sloan et al[115] published the first human phase I study that used the escalating dose of hyperthermia to assess the safety and efficacy of the procedure in patients with rGBM. The median OS was 10.5 months after LITT, which was increased compared with historic control by 3 to 9 months.[54] These findings demonstrated that LITT was a feasible and safe treatment modality for rGBM, but further RCTs are required to evaluate the efficacy of this novel modality.

Nuclear medicine thermal therapy (NMTT): Nuclear medicine has generated a new promising arsenal for rGBM therapy. This has been mainly driven by biotechnologies such as radioimmunotherapy, radiopeptide therapy and radionanoparticles. Nuclear medicine therapy typically uses specific vectors to deliver radioactivity to the tumor site. In the rGBM field, β particle emitter's isotopes (I^{131}, Y^{90}, $Re^{186/188}$, and Lu^{177}) are coupled with nanoparticles, monoclonal antibody, or peptides. These radio carriers produce targeted internal RT. Many clinical trials demonstrate the efficacy and safety of nuclear medicine approach, but these have only been assessed in phase I or II trials. These results need to be strengthened and phase III trials are necessary to confirm the emerging place of nuclear medicine in the therapeutic arsenal against rGBM.[116]

Chimeric antigen receptor (CAR) T-cell therapy: Cytotoxic T lymphocyte collected from a patient can be genetically modified to express a CAR specific for an identified tumor antigen (TA). These CAR T cells can then be readministered to the patient to identify and eliminate cancer cells. However, there is still a long way ahead for CAR T-cell therapy before it becomes a standard of care for the treatment of patients with GBM/rGBM. Most clinical trials have proven that CAR T cells as a monotherapy are not particularly effective in solid tumors due to numerous immune escape mechanism utilized by cancer cells.[117] This appears to be also true for GBM, which additionally presents its own unique challenges to overcome. Among them, optimization of CAR T-cell delivery into the brain is an important obstacle to overcome.

Combination Therapies

Given the heterogeneity of rGBM, it appears that combination treatment may be more effective than monotherapy

alone. The prevalence of certain mutation at the time of recurrence may play a role in deciding which combination therapy is most effective. However, combining therapy may subject a patient to more treatment side effects. Taslimi et al[118] did a systematic review and network meta-analysis on treatments from randomized control trials to assess the effect on OS and PFS for rGBM. They found that combination treatment with TTF and VEGF inhibitor ranked first in improving OS ($p = 0.80$) and concomitant anti-VEGF and lomustine treatment was superior to lomustine alone for extending PFS (HR = 0.57; 95% CI: 0.41–0.79), ranked first in improving PFS compared with other included treatment ($p = 0.86$). A phase I clinical trial (ClinicalTrial.gov identifier: NCT02770378) is underway to assess the safety of the coordinated undermining of survival paths by nine repurposed drugs (aprepitant, auranofin, captopril, celecoxib, disulfiram, itraconazole, minocycline, ritonavir, and sertraline) combined with metronomic TMZ (CUSP9v3 treatment protocol) for rGBM.

Treatment of Elderly Patients with rGBM

The management of rGBM in elderly patients poses further challenges as the patients have limited life expectancy. It generally depends on the extent of disease and patient condition and is particularly difficult in the elderly subgroup, as they are a very heterogenous population.[118] Age, although associated with comorbidities and overall frailty, does not necessarily reflect the patient's physiologic reserve or functional capacity[120] and thus should not preclude active management of recurrence. Performance status, being the next most important prognostic factor for survival,[121] must be factored heavily into the decision-making process, as it generally reflects the patient's ability to receive any form of active treatment. The factors associated with worse prognosis are poorer performance status and comorbidities. Recurrences in isocitrate dehydrogenase (IDH) wild-type GBM had further poorer prognosis as compared with the IDH mutant type.

Local treatment, mainly surgery, seems to be the most effective salvage strategy in selected elderly patients with KPS $\geq$ 60%. Elderly patients in good clinical status have higher survival as compared with the patients in poor clinical status of the same age group.[122] Quick et al[123] reported that survival after second surgery in elderly patients with KPS of <80% was 8.6 months versus 15.6 months in patients with higher KPS ($p = 0.047$). Socha et al[124] reported that elderly rGBM patients with poor KPS may also benefit from active treatment, as the active treatment approach more than doubled the median postprogression survival (PPS) in these patients (21 vs. 9 weeks with best supportive care, $p = 0.014$). However, local treatment (surgery and/or RT) did not result in better outcomes compared with chemotherapy, probably due to postoperative complication following repeat surgery. Thus, chemotherapy seems to be the optimal therapeutic approach for this special subgroup. In conclusion, elderly patients in good KPS had better outcomes with local treatment (surgery and/or RT), whereas elderly patients in poor performance status chemotherapy seem to be a better salvage option.[122,124]

Current clinical trials: Cancer stem cells are likely to be pivotal in rGBM and effort should be made to evaluate whether specifically targeting this tumor cell population prevents tumor recurrence,[125] and is promising for eradication of the source of recurrence. Using a Clinical Laboratory Improvement Act (CLIA) certified and College of American Pathologists (CAP) accredited drug response assay, a phase III clinical trial is currently testing tailored and personalized chemotherapy versus nonguided chemotherapy in rGBM patients (NCT03632135). Other ongoing phase III clinical trials for evaluating the efficacy of certain regimen in rGBM are autologous dendritic cell/tumor antigen vaccine (ADCTA) for adjuvant immunotherapy in standard treatment of rGBM (NCT04277221), intermittent sunitinib (NCT03025893), disulfiram (NCT02678975), multiple regimens (TMZ, lomustine and regorafenib; NCT03970447), and BEV versus dose-dense TMZ, followed by BEV (NCT02761070).[125]

Conclusion

The treatment of rGBM should be individualized, depending on the prognostic factors. Re-surgery, re-irradiation, and systemic chemotherapy provide only short-term disease control and modest survival. Re-surgery should be considered in patients with rGBM located in noneloquent regions in a younger-age patients with a good preoperative KPS status. Patients with smaller-size tumor in eloquent location and recurrence after long time of primary RT should be considered for re-irradiation along with chemotherapy. MGMT methylation status further decides between TMZ and BEV. Nitrosourea should be considered in situations where BEV is either contraindicated or unavailable. Novel treatment techniques like Novo TTF and immunotherapy hold promise to impart better survival without compromising on the quality of life. In elderly patients with rGBM, hyperfractionated accelerated radiotherapy (HFRT) is a valuable option proven equivalent to TMZ, and MGMT promoter methylation guides the choice of single-modality therapy. The addition of TMZ to HFRT yields an improved OS in the elderly patients.

Conflict of Interest
None declared.

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