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Treatment of recurrent glioblastoma: state-of-the-art and future perspectives

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ABSTRACT

Background: Almost all patients affected by glioblastoma experience recurrence of the disease.

Areas covered: Management of recurrent glioblastoma is a clinical challenge, and several elements should be taken into consideration when making treatment choice. Loco-regional treatments may be the best treatment approach in selected cases while systemic therapies or supportive care alone are necessary in other patients. Unfortunately, few drugs have shown clinical activity in this setting. This lack of effective treatments has made recurrent glioblastoma a disease orphan of an effective approach.

Expert opinion: Results of recent clinical trials offer interesting perspectives and may controvert this axiom.

Key words: glioblastoma, recurrent glioblastoma, chemotherapy, bevacizumab, regorafenib, immunotherapy, immune-checkpoint inhibitors, systemic therapy, target therapy.

Article highlights:

- The management of recurrent glioblastoma has several approaches
- Loco-regional or systemic treatment may be proposed in these patients
- Multidisciplinary discussion in a high-volume centre should be performed in each new diagnosis of glioblastoma relapse
- Some new agents under investigation show promising activity
- Assessment of a novel agent in fully powered randomized trial should be performed

1. INTRODUCTION

Among central nervous system (CNS) primary malignancies, glioblastoma is the most frequent tumour in adults. According to the 2016 WHO classification, glioblastomas can be divided into two main subgroups. The IDH wild type tumours (90%) represent de novo glioblastomas and frequently could be diagnosed in patients over 55 years of age. The IDH-mutant tumours correspond to secondary glioblastomas and are generally diagnosed in patients younger than those with primary glioblastoma. Furthermore, these patients have a known clinical history of prior lower grade diffuse gliomas [1].

Prognosis depends on several factors including; age, extent of resection and performance status. Patients with IDH mutated tumours and/or MGMT methylation have longer survival rates due to an improved benefit from therapy [1]. The standard approach for newly diagnosed glioblastoma is represented by surgery followed by temozolomide (TMZ) concomitant with and adjuvant to radiotherapy [2,3]. The combination between maintenance TMZ and Tumor –treating fields (TTFields) which consists of a low-intensity alternating electric fields provided to the tumour has also been investigated [4].

In elderly patients the standard approach consists of administration of a short course of radiotherapy with the addition of temozolomide [5]. Unfortunately, glioblastoma generally recurs after a variable time of response [6,7]. Principal causes of death are related to tumour dissemination including invasion of the brainstem more than severe mass effect [8].

Compared to newly diagnosed GB, the management of recurrent disease is less standardized and different approaches should be considered including systemic agents (chemotherapy, target therapy) or loco-regional treatments (radiation therapy and surgery).

There are many reasons for the lack of effective treatments in recurrent glioblastoma. The intrinsic resistance of tumours cells, the molecular heterogeneity, the reduced intra-tumour concentration of several effective treatments due to the blood-brain-tumour barrier, the difficult prediction of clinical efficacy of compounds tested in small clinical trials and the lack of interest by pharmaceutical agencies due to the low incidence of CNS malignancies are all possible reasons [6,9].

However, despite these limitations, some important steps have occurred in the recent years, and some agents seem to show promising activity [6,9]. In this review, we discuss available treatment approaches in recurrent glioblastoma, potential future perspectives and efficacy assessment of these compounds in clinical trials (Figure 1).

2. MEASURING OUTCOME IN CLINICAL TRIALS

Assessment of clinical efficacy in glioblastoma is a complex issue: differently from other solid malignancies some clinical endpoints (such as response rate) may be not useful in glioblastoma [10]. To date, overall survival (OS) is still the best endpoint for the assessment of a specific drug or intervention in recurrent glioblastoma.

The overall response rate (ORR) is an endpoint and clinical efficacy outcome adopted in some phase II trials. The assessment of ORR may be complicated due to several issues.

The assessment of tumour dimensions is usually done in other solid malignancies. However, in CNS tumours it could not reflect the effective response to treatment. This mainly because pseudoprogression may occur after chemo-radiation treatments. The assessment of tumour

dimensions is generally associated to an assessment of clinical conditions, and corticosteroids uptake (which may reflect tumour associated oedema). The evaluation of all these factors results in a reliable assessment of the response to treatment [10-14].

The dimensional margins of the tumour could not reflect imaging. Indeed, peripheral cells have a different genomic assessment associated to infiltrative proprieties and altered RNA expression. The modified mutation profile of peripheral cells could be also related to a different pattern at imaging [15]. Patients treated with the angiogenesis inhibitor bevacizumab could experience a fast reduction of vessel permeability and contrast enhancement resulting in a pseudo-response. In addition, patients relapsed after bevacizumab or other angiogenesis inhibitors may develop non-enhancing lesions [16]. On the other hand, patients treated with TMZ may experience radiological pseudo-progression after radiotherapy, especially in the presence of the methylation of the O-6-methylguanine-DNA methyltransferase [14].

The MGMT gene encodes a key enzyme involved in DNA repair. Patients missing this enzyme due to methylation have improved benefit from the administration of temozolomide [14]. The pseudoprogression is a known pattern of response to immune-checkpoint inhibitors in solid tumours, while its incidence in glioblastoma is still unknown [18].

To avoid the limitations concerning these radiological patterns and to integrate clinical information on the assessment of tumour response, specific assessment criteria have been validated. Nonetheless, the evaluation of ORR as only clinical efficacy outcome may be limitative in phase II clinical trials [10-14].

Progression-free survival (PFS) is a distinct endpoint which has the advantage of being influenced only by the treatment received, while OS also reflects subsequent treatments received including re-surgery or re-irradiation. In particular, PFS rate at the pre-specified time of assessment is often used in clinical trials. However, only few studies evaluating the

correlation between PFS and OS provided information about the correlation between these two endpoints [19-21].

In the absence of valid and reliable surrogate endpoints, OS (expressed also as rate at 6 or more months after study start) still remains the best endpoint of clinical trials making complex the assessment of the efficacy of novel compounds in phase II clinical trials.

3. SURGERY

Repeat surgery at the time of glioblastoma recurrence is a possible treatment option. Patients more likely to benefit from this approach are patients with good performance status and smaller and superficial tumour with more possibility to achieve a complete resection. Time of recurrent disease and molecular assessment of the disease may also be crucial elements to select these patients.

It is important to note that no randomized trial has assessed this approach as a comparison between surgery and chemotherapy (or another systemic treatment) is not feasible from an ethical standpoint.

Two meta-analyses have investigated surgery as a treatment approach in recurrent glioblastoma [22,23]. The first study assessed eight observational studies for a total of 1906 patients with glioblastoma who underwent primary surgery and 709 patients with recurrent glioblastoma who were undergoing secondary surgery [22]. The pooled Hazard Ratio (HR) clearly showed a longer OS for patients receiving surgery at the time of recurrence (HR: 0.722; $p < 0.001$) [22]. Of interest, more recent studies were associated with an improved survival advantage compared to older ones [22]. The second meta-analysis aimed to assess the impact of the extent of resection of re-operation on prognosis in patients treated with TMZ [23]. The authors selected nine studies for a total of 1507 patients with glioblastoma

and 1335 patients treated with surgery at the time of recurrence. Among these studies, OS after repeat surgery ranged from 8 to 13 months [23].

The authors find that maximal resection at re-operation was significantly prognostic for longer OS (HR 0.59, p< 0.1). Radiographic confirmed gross total resection was the most prognostic variable related to the extent of surgery and was associated to longer OS (HR 0.52, p< 0.01) [23].

It is possible that the inclusion of retrospective studies evaluating patients with smaller tumour size and more superficial masses may, in part, explain the survival advantage emerged by this analysis. This selection bias may have influenced the results observed in both meta-analyses discussed.

The selection of patients more likely to benefit from this approach is another key element to consider. Indeed, re-operation is not free from complications, which can sometimes be serious. Complications related to re-surgery occur in 33% of patients with a mortality rate of 2.2%, depression (20%), seizures (10%), intracranial bleeding/systemic infection (4%) and worsening of neurological symptoms (18%) were the most frequent events [24].

To date, two preoperative scales have been validated to estimate the prognosis of patients undergoing to re-operation [25,26]. The NIH (National Institutes of Health) scale assesses Karnofsky performance status (> or ≤80), tumour volume (< or ≥ 50 cm3) and involvement of critical brain regions [25]. A second scale based on Karnofsky performance status and ependymal involvement has been developed to avoid confounding and subjective assessment of tumour volume and the critical region as required in the NIH scale [26].

A longer interval after primary surgery (> 6 months) and a good Karnofsky performance status (defined as > 70%) or Eastern Cooperative Oncology Group score are two critical and independent variables related to re-surgery outcome [27-32].

The presence of MGMT methylation could recognize a subgroup of patients more likely to benefit from a re-surgery [33-35]. However, this finding may not reflect a direct effect of re-surgery as these patients are associated with improved prognosis and benefit from TMZ. However, the achievement of a safe maximal resection seems to be related to improved prognosis regardless of MGMT status [34,35].

Few data are available about the optimal management after surgery. Adjuvant treatment should be an option [36,37], but their exact impact on prognosis still remain unclear. The administration of bevacizumab after repeat surgery showed no statistically significant improvement of OS [29]. Similarly, in patients receiving TMZ after surgery, the extent of surgery is the best prognostic variable [38,39].In conclusion, re-operation should be included in the treatment algorithm of recurrent glioblastoma. When technically safe and associated with a feasible total resection, it should be proposed, especially in patients with good performance status.

Optimal management after surgery is still controversial. Clinical and biological variables such as age, time to tumour relapse and MGMT status should be considered; however, their impact on prognosis seems of secondary importance compared to the achievement of total resection. Prospective studies assessing surgery on recurrent glioblastoma with or without experimental drugs are ongoing and may represent an option for selected patients (NCT04406272, NCT02394626). Studies employing re-surgery allow for the assessment of biological effects of previous administered drugs through pathological and biological assessment of resected tumour (phase 0 studies). In particular, the RESURGE trial (NCT02394626) is currently investigating the optimal management in patients with recurrent glioblastoma. In this trial patients with recurrent disease are randomized to receive surgery followed by adjuvant treatment versus second line alone.

4.0 RE-IRRADIATION

As the majority of recurrences occur within the high dose radiation field (90-95%), re-irradiation is generally poorly considered as a treatment option due to the high risk of toxicity.

However, as observed by Brandes AA et al., a notable percentage of patients (especially patients with MGMT methylation) experience recurrence out of the radiation field (up to 20%) [14].

Similar to re-surgery, the adequate selection of patients suitable for re-irradiation is a key issue. Age, performance status, target volume, time to progression, type of progression (monofocality versus multifocality), and site of recurrence are essential elements to consider. These factors are crucial as they can also differentiate the type of treatment provided (stereotactic versus hypo fractionated versus standard treatment) and dosage provided.

To date, two prognostic scores have been validated to estimate the prognosis of patients undergoing to re-irradiation. The first prognostic score is composed of an assessment of histology (glioma grade II, III or IV), age (< or > 50 years), and time between initial radiation therapy and the second course of radiation (< or > 12 months) [40]. The second prognostic score consider: age, initial histology, and performance status (Karnofsky< or > 70) [41]. Through this score, patients can be divided into three main categories with a predicted post recurrence survival of 14.2 (good), 9.1 (intermediate), and 5.3 (poor) months [42].

The majority of studies assessing re-irradiation were retrospective series. A large meta-analysis evaluated 50 studies for a total of 2095 patients with recurrent glioblastoma [43]. The authors concluded that re-irradiation was associated with a 6 and 12 month OS of 73%

and 36%, respectively. It is important to note that the majority of studies assessed were retrospective (40/50) and that only 42% of studies included were of good/fair quality [43].

A systematic review carried out considering 29 studies assessed several issues related to re-irradiation, including clinical outcomes achieved with different radiation techniques [44].

The authors concluded that target volume is a key element to consider before planning radiation treatment. A small volume (< 12.5 mL) can benefit from radiosurgery as salvage treatment, while hypo-fractionated regimens should be proposed to patients with lesions < 35 mL. Conventionally fractionated radiotherapy should be proposed in a larger volume (up to 50 mL) [44].

The same systematic review assessed concomitant or sequential administration of chemotherapy or bevacizumab. Considering that very few studies investigated this issue, it has been suggested that TMZ does not improve OS compared to radiation therapy alone [44]. Bevacizumab is an agent able to reduce the amount of oedema and it has been administered after radiation therapy to reduce the risk of radionecrosis. However, this hypothesis has not been confirmed and the administration of bevacizumab has been related to an increased risk of toxicity (up to 40% high-grade toxicity) without significant improvement of PFS and OS [44].

It should be also emphasized that few prospective data are available in this field. In a phase II trial 182 patients with recurrent glioblastoma were randomized to receive bevacizumab alone or in combination with radiation treatment (35 Gy in 10 fractions). The combination of radiation therapy and bevacizumab prolonged PFS of these patients without significant improvement in OS [45].

Regarding treatment toxicity, it is well known that some organs are at high risk of radiation toxicity. The dose received by optic pathways and brainstem must be carefully assessed. The risk of radionecrosis should also be considered. Several studies reported a variable incidence of radiological diagnosis of radionecrosis (from 4% to 31.3%) [43,44]. These same studies did

not specify if radionecrosis was associated with neurological symptoms or the need of steroids.

Re-irradiation may be an option for patients with recurrent glioblastoma. The risk of toxicity should be estimated considering the previous radiation field, site of recurrence, and target volume. This last factor is a key element as dosage received and modality of treatment should depend mainly on tumour volume (less than 12.5 mL required 12-15 Gy in single fraction; 12.5 mL – 35 mL should be treated with 25 Gy in about 5 fractions and masses larger than 35 mL should receive 36 Gy in about 20 fractions) [44]. Of course, the site of recurrence also assumes critical importance as distant recurrence could allow an increase of total dosage provided why reduced dosage should be provided in local recurrence to reduce the risk of radionecrosis [44]. Age, performance status, histology, and the interval between radiation treatments are other elements to consider.

5.0 TEMOZOLOMIDE RECHALLENGE

Treatment with concomitant and adjuvant TMZ represents standard management of glioblastoma [2]. At the time of recurrence, rechallenge therapy with TMZ could be proposed [46-53]. To date, this strategy has been assessed by small phase II trials [46-49]. These trials assessed alternative schedules of TMZ administration.

It is well established that patients with methylated MGMT experience more benefit from TMZ [50]. This axiom is far from being well defined in recurrent glioblastoma. Only one prospective trial [49] demonstrated a clear association between MGMT methylation and improved clinical outcomes. Of note, this was the only trial performing a prospective assessment of MGMT status in all patients enrolled [49]. Thus, it could be necessary to obtain a novel evaluation of MGMT status (before treatment starting) to confirm its prognostic and predictive role in recurrent glioblastoma.

Another issue to consider could be the interval of time between the recurrence and adjuvant treatment. The RESCUE trial [47] suggested that patients experiencing recurrence during the first six months of adjuvant TMZ, as well as patients with recurrence after two months from the end of adjuvant TMZ, had improved clinical benefit from rechallenge TMZ [47].

These findings seem to be partially confirmed in retrospective series.

Franceschi E. et al. demonstrated that patients with a treatment-free interval of 5 or more months from the end of adjuvant TMZ had improved survival and progression-free survival [51]. Of note, this benefit was achieved regardless of MGMT status. Similarly, another retrospective study suggested an improved six months PFS in patients with a treatment-free interval of 3 months or more [52]

Among methylated MGMT patients enrolled in DIRECTOR trial survival and PFS were significantly longer in patients with treatment-free interval longer than two months [49].

Dose intensity of TMZ may be another critical element to consider. In a large randomized clinical trial 447 patients with recurrent glioblastoma were randomized to receive PCV, TMZ (standard schedule 200 mg/mq D1-5) or alternative TMZ schedule (100mg/mq for 21 days). The 21 days schedule was inferior to the standard schedule [54]. Re-challenge with TMZ could be an option in all patients with recurrent glioblastoma, especially in those with longer treatment failure interval. MGMT status may have a role in the patient's selection.

6.0 OTHER SYSTEMIC TREATMENTS

Several agents have been tested in progressive glioblastoma. To date, some agents have shown promising clinical efficacy [55-77] (table 1).

Chemotherapy, targeted agents, and immune-checkpoint inhibitors have been assessed in phase II and randomized phase III trials with different outcomes.

6.1 CHEMOTHERAPY

Chemotherapy was the standard treatment option for patients with recurrent glioblastoma. Nitrosoureas are the most administered agents [55-61,67, 70,71,73].

Lomustine is an orally available agent and represents the standard comparative arm in randomized clinical trials. Lomustine has haematological toxicity as the most important side effects and resulted in an OS ranging from 5.6 to about 10 months in clinical trials [55-61,72]. Lomustine has mainly been investigated in association to procarbazine and vincristine as part of the PCV regimen. As vincristine does not cross the blood brain barrier and due to the very limited clinical activity of procarbazine in recurrent glioblastoma the single agent lomustine becomes a standard treatment for the management of recurrent glioblastoma[78]. Notably, differently from other agents, lomustine has been tested in a large randomized phase III trial with/without bevacizumab. Median OS achieved with lomustine alone was 8.6 months while local progression free survival was 1.5 months [55]. The combination between TMZ and lomustine has been recently tested in newly diagnosed MGMT methylated glioblastoma patients [79]. In this population, the combination resulted in OS improvement (48.1 vs 31.4 months)[80].

Another nitrosourea, fotemustine, could be a treatment option in patients with recurrent glioblastoma.

Two trials investigated the role of this agent. Both these studies were phase II trial assessing fotemustine alone [68] or as comparator treatment of bevacizumab [66]. Administration of this agent resulted in OS of 6-8.7 months.

Systemic chemotherapy has been evaluated in small phase II trials [62-65, 67] alone or in combination with other agents such as bevacizumab [62,63] or erlotinib[65]. When added to

systemic bevacizumab the administration of carboplatin and irinotecan did not seem to add additional OS benefit, indeed OS achieved with this combination reached about 8 months [63,69].

Systemic chemotherapy different from nitrosoureas does not represent the standard treatment option.in patients with recurrent glioblastoma. It could represent an option in motivated patients with good performance status progressed to other treatments. However, the effective clinical impact of systemic chemotherapy in advanced lines of treatment is far from being defined [76].

6.2 BEVACIZUMAB

The vascular endothelial growth factor (VEGF) is the ligand of vascular endothelial growth factor receptors (VEGFR). Interaction between ligand and receptors activates an intracellular cascade leading to the promotion of vascularization and angiogenesis. The promotion of angiogenesis is a known strategy adopted by tumours to promote their development and progression.

Bevacizumab is a humanized monoclonal antibody targeting VEGF-A. The clinical impact of this agent in glioblastoma has been assessed in different clinical trials.

In 2009, Friedman et al. assessed bevacizumab alone or in combination with irinotecanb [69]. Overall survival was 9.2 and 8.7 in monotherapy and combination arms, respectively. No statistically significant difference was assessed in terms of PFS (6-months PFS was 42.6% and 50.3% in monotherapy and combination arms) and ORR (28.2% and 37.8%) [69].Similarly, Kreisl et al tested bevacizumab in patients with recurrent anaplastic glioma obtaining an OS of 12 months and a 6-months PFS rate of 20.9%.[80]

Although this was the first randomized (phase II) trial showing the encouraging activity of bevacizumab, several concerns emerged from this study. First of all, the missed comparison

with the standard treatment arm represented by nitrosoureas. Thus other clinical trials investigated this agent.

Other trials assessed bevacizumab alone [62] or in combination with chemotherapy (including carboplatin and irinotecan) [63]. Both these studies seemed to suggest that the addition of chemotherapy did not provide additional benefit to bevacizumab in patients with recurrent GB.

The BELOB trial was a three arms phase II trial assessing lomustine, bevacizumab, or a combination of both in patients with recurrent glioblastoma [56]. This study showed that OS and clinical outcomes of lomustine and bevacizumab were similar, while combination treatment seemed to improve the survival rate of patients enrolled [56]. These promising results were not confirmed by another phase II trial assessing bevacizumab alone or combination of bevacizumab plus lomustine [58]. This study failed to show a survival benefit for patients receiving combination treatment [58]. However, it should be noted that the dose of bevacizumab adopted in the combination arm was 5 mg/mq compared to the standard dose of bevacizumab in glioblastoma (10 mg/mq). Specific subgroups of patients (younger with high expression of the chitinase like protein YKL40) seem to derive harm from the administration of bevacizumab while other (including patients with MGMT and IDH mutation) may get more clinical benefit [81-83].

It should be also highlighted that the administration of bevacizumab results in a reduced enhancement on imaging, which may appears as a response to treatment [16,19]. The altered contrast intake seen on CT scan or MRI reflects the angiogenesis inhibition related to bevacizumab and is not necessarily related to response to treatment [16,19].

TAMIGA trial was a phase II randomized clinical trial in which patients with newly diagnosed glioblastoma received radiation therapy plus temozolomide with bevacizumab followed by bevacizumab as maintenance treatment [84,85]. At time of progression patients were randomized to receive CCNU plus Bevaziumab or CCNU plus placebo. The trial failed to show

a significant difference in terms of overall survival among study arms. However, no detrimental effect has been observed [84,85].

A phase III trial compared lomustine to lomustine + bevacizumab treatment in 437 patients with recurrent glioblastoma [55]. This study fails to meet its primary endpoint, which was the OS. In particular, patients receiving the combination, treatment had an OS of 9.1 months compared to 8 months in patients treated with lomustine (Hazard Ratio 0.95, 95% CI, 0.74-1.21. P= 0.65). The addition of bevacizumab resulted in 63.6% of high-grade adverse events (AEs), while grade 3 to 5 AEs occurred in 38.1% of patients treated with lomustine [55].

The AVAREG compared single agent bevacizumab to fotemustine in patients with recurrent GB. This trial suggested a similar clinical outcome for patients receiving these two agents. In particular, mOS and six-months PFS were: 7.3 and 8.7 months and 26.3% and 10.7% in patients receiving either bevacizumab or fotemustine, respectively [66].

On the basis of these studies, it could be summarized that the combination of chemotherapy (either nitrosoureas or other cytotoxic agents) and bevacizumab does not improve survival or other clinical endpoints. On the contrary, the toxicity of these combinations is significantly higher than those detectable in monotherapy arms.

Bevacizumab seems to be associated with similar clinical outcomes of other systemic agents, including lomustine. Thus patient's preference, comorbidity assessment and different toxicity profile (hypertension, thrombosis, pulmonary embolism, bowel perforation, platelet count decrease, proteinuria with bevacizumab) should drive the choice of this agent as treatment adopted at the time of glioblastoma recurrence. Finally due to a direct effect on tumour vascularization, the permeability of blood-brain barrier could be altered influencing intratumoral concentration of drugs provided at time of bevacizumab failure and clinical outcomes achieved in lines of therapy received after bevacizumab [83]. However, long real word studies seem to not confirm this issue as the OS of patients receiving bevacizumab is not modified by the line in which bevacizumab is provided [86,87].

6.3 TARGET AGENTS AND TYROSINE KINASES INHIBITORS

Several agents targeting different pathways have been tested in recurrent glioblastoma. In particular small molecules targeting the VEGF/VEGFR pathways failed to show a significant improvement in clinical outcomes compared to standard chemotherapy [57,60,61]. The epidermal growth factor receptor (EGFR) has been identified in about 40% of primary glioblastoma [75]. Unfortunately, studies evaluating gefitinib and erlotinib alone or in combination with chemotherapy [65,67,74,75] failed to show a significant benefit. Similarly, a study assessing an inhibitor of the PI3K/Akt pathway did not show clinical improvement [59].

Recently, results of a phase II trial seem to show regorafenib as an agent able to improve survival and other clinical outcomes of patients with recurrent glioblastoma [73].

Regorafenib is a tyrosine kinase inhibitor. It can interact with several pathways, including VEGFR, TIW2, KIT, RET, RAF1, BRAF, PDGFR, and FGFR. In a phase I trial, regorafenib was administered in combination with cetuximab showed a promising clinical efficacy in one patient with advanced glioblastoma [88].

In the REGOMA trial, 124 patients with recurrent glioblastoma were randomized to receive regorafenib or lomustine [73]. The primary endpoint of the study was overall survival while PFS, and the percentage of patients achieving disease control were secondary endpoints. The median OS was 7.4 months and 5.6 months in patients receiving regorafenib and lomustine, respectively (HR 0.50 95% CI 0.33-0.75; p=0.0009). The six-months PFS was 16.9% and 8.3% (HR 0.65; 95% CI 045-0.95), while disease-free control was obtained in 44% and 20% of patients receiving regorafenib and lomustine respectively [73]. The main high-grade toxicity of regorafenib consisted of fatigue, hand-foot syndrome, lipase increase, bilirubin increase, and lymphocyte count decrease.

Of note, statistical design of this study was planned through a screening design aimed to assess whether regorafenib showed more probability to improve overall survival compared to lomustine. This means that this phase II study was not powered enough to estimate an effective advantage in OS but was aimed to a preliminary assessment of regorafenib efficacy. Authors adequately specify this issue and concluded that regorafenib showed promising efficacy in patients with recurrent glioblastoma but a phase III trial is needed to confirm this benefit. In addition, some concerns about regorafenib efficacy are related to previous reports in which regorafenib failed to show a significant clinical improvement as well as to the short OS observed with lomustine, which is significantly different from what observed in other clinical trials [89]. Novel systemic agents are under investigation. Randomized phase III trials are currently assessing the role of different approaches. (Table 2).

Two different randomized clinical trials are evaluating two tyrosine kinases inhibitors. Sunitinib is multi-kinases inhibitors, which acts mainly on VEGFR and angiogenesis. An alternative high dose schedule is currently under evaluation in comparison to lomustine in patients with recurrent glioblastoma.

The NCT03970447 trial is currently assessing two different approaches: in comparator arm patients treated with radiation therapy and TMZ after surgery receive standard TMZ as maintenance treatment and lomustine at time of recurrence. The experimental arm has as main difference the administration of regorafenib as maintenance treatment and as systemic agents at time of recurrence.

6.4 IMMUNOTHERAPY

In recent years some studies have investigated the role of immune-checkpoint inhibitors in recurrent glioblastoma. Inhibitors of the Programmed Death Ligand 1 or Receptor (PD-L1

and PD-1 inhibitors) and inhibitors of the Cytotoxic T Lymphocytes-Antigen 4 (CTLA4) represent immune-checkpoint inhibitors. The inhibition of these receptors resulted in restored immunity against cancer cells. In a phase I study assessing nivolumab (a PD-1 inhibitor) and ipilimumab (a CTLA4 inhibitor), nivolumab monotherapy showed a promising safety profile [90].

The Checkmate 143 phase III cohort compared nivolumab or bevacizumab in 369 patients with recurrent glioblastoma. The primary endpoint was OS, which was not met at the final analysis [91]. Furthermore, the response rate was higher in bevacizumab arm (23.1%) as compared to nivolumab arm (7.8%); however, responses in the nivolumab group were significantly longer.

Of note, a subsequent analysis of this study showed that two subgroups of patients might experience significant benefit from the administration of immune-checkpoint inhibitors. Patients with methylated MGMT and patients with no corticosteroids use are more likely to benefit from these agents. In these patients, m OS was 17.0 months with nivolumab and 10.1 months with bevacizumab [91]. A phase II study assessing nivolumab in patients with methylated MGMT and recurrent glioblastoma is currently ongoing and will provide important information on this issue (NCT03743662).

Notably, the PD-1 inhibitor nivolumab has been tested in patients with newly diagnosed glioblastoma. In particular, two large phase III trial assessed nivolumab in association to radiotherapy and concomitant temozolomide in patients with MGMT methylation (Checkmate 548) orin association to radiation therapy alone in patients without MGMT methylation (Checkmate 498) without significant PFS (Checkmante 498 and 548) and OS (Checkmate 548) improvement compared to standard of care [92].

Also the PD-1 inhibitor pembrolizumab and the PD-L1 inhibitor atezolizumab have been tested in recurrent glioblastoma showing a modest clinical activity [93,94] The peripheral CD4+ cells, the hyper mutated tumour status and other alterations including molecular

anomalies and different immune-expression signatures (influencing immune-contexture) are key issues which may influence response to immune-checkpoint inhibitors [92,94,95]. Finally these agents showed promising activity when adopted as neo-adjuvant agents, suggesting that the early administration of immune-checkpoint inhibitors could result in improved clinical outcomes [96, 97].

Other strategies under investigation are the administration of vaccines, immune-modulatory molecules as well as the viral therapy.

The rindopepimut is a peptide EGFR vIII vaccine that failed to show significant clinical activity when adopted as single agents [98]. On the other hand, promising results emerged when this agent has been combined with bevacizumab in recurrent GB [99]. Oncolytic viruses are agents able to deliver specific genes through viral vectors. The Ad-RTS-hIL-12 is an adenoviral vector encoding for interleukin-12, which is currently under investigation in a phase II clinical trial (NCT04006119). Other oncolytic viruses are able to perform a direct cytolyses on cancer cells such as the PVSRIPO (an attenuated polio-rhinovirus chimera) and DNX-2401 (an adenovirus) are under investigation with immune-checkpoint inhibitors in phase II clinical trials (NCT02798406, NCT02986178).

7. CONCLUSION

Local treatments such as surgery and radiation therapy or systemic chemotherapy/biological agents are possible approaches for recurrent glioblastoma. To date, the standard therapeutic approach for these patients is far from being well identified and adequate selection of patients is mandatory to select best treatment option. A patient's performance status, time to recurrence, site of recurrence and patients' preference are key elements to consider. Nonetheless, prognosis of these patients remains poor requiring the development of new drugs and treatment strategies for these patients. Thus, these patients should be

treated and assessed in high-volume centres and enrolment in clinical trials should be encouraged.

8. EXPERT OPINION

The molecular assessment of the disease could be a key issue to consider and it is possible that the future pathological classification of central nervous system tumours will attribute a critical importance to this element.

Some genes, including the isocitrate dehydrogenases and the MGMT, may help to select patients with more favourable prognosis and (in the case of MGMT) to select patients more likely to benefit from TMZ.

Of interest, new trial designs named adaptive platform trials allow to test several compounds or interventions in a single disease through a perpetual manner. These platforms are able to provide several data about different compounds relatively quickly. Compounds providing clinical efficacy in a specific subpopulation of patients could be also re-tested in this specific population through a response-adaptive randomization.

The Adaptive Global Innovative Learning Environment for Glioblastoma (Agile) is a novel adaptive trial platform in which novel compounds are tested through a two stage process: first: a Bayesian adaptively randomized stage assessing the impact of the novel compounds on overall survival as compared with a common control and second: a fixed randomized assessment to confirm the results observed in first step [100].

Similarly, the individualized screening trial of innovative glioblastoma therapy (INSIGhT) proposes a trial platform tailored on the basis of molecular assessment of the disease [101].

In conclusion, the management of recurrent glioblastoma could benefit from treatment approaches including loco-regional treatments or systemic drugs. The molecular assessment

of the disease is a critical element to impact our clinical choices, and will likely assume further importance in the coming years. To date, immune-checkpoint inhibitors and immunotherapy failed to provide significant results in patients with recurrent disease, however novel immunological approach (oncolytics and vaccines) are under investigation and it is possible that the results of these studies will provide further active treatment options for patients with recurrent glioblastoma. Patients with recurrent glioblastoma and other primary central nervous system tumours should be referred to high-volume centre in order to improve clinical outcomes and to promote enrolment in clinical trials [102].

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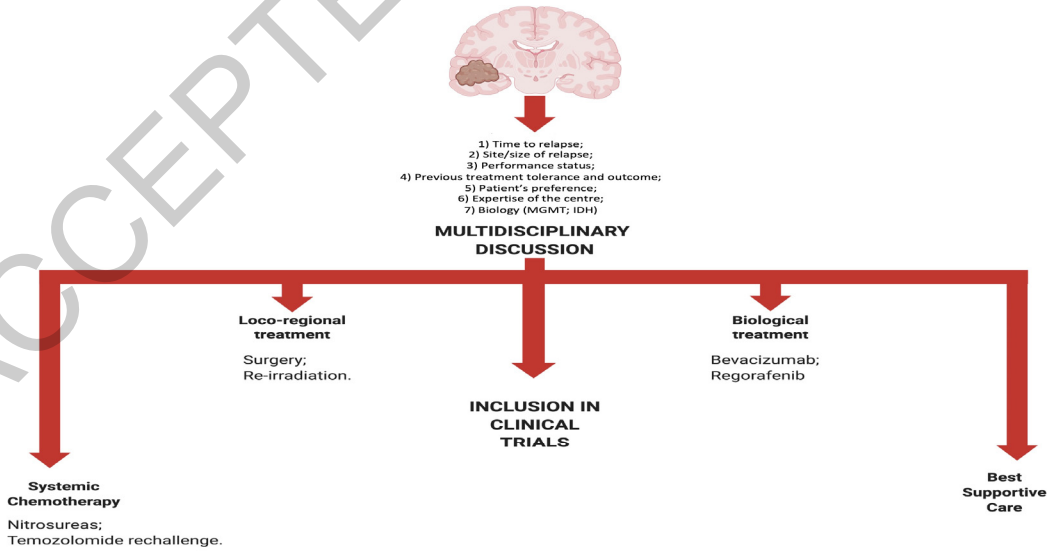
Figure 1



Trial	Year	Phase	Treatment arms	Main findings
Vick W [53]	2017	III	A) Lomustine + Bevacizumab B) Lomustine	Similar mOS for treatment arms: *mOS: 9.1(A) vs 8.6 (B) months*

In this figure we summarized available treatments approach for recurrent glioblastoma. In particular, we highlighted some clinical and pathological variables that should be considered and the importance of multidisciplinary assessment before final decision.

Table 1

An overview of clinical trials discussed in text. mOS: median overall survival.

Taal W [56] BELOB	2014	II	A) Lomustine + Bevacizumab B) Lomustine C) Bevacizumab	9 months OS improved in arms A and B but no C (Bevacizumab) *9 months OS: 59% (A) 43% (B) 38% (C)*
Duerink J [57]	2018	II	A) Axitinib + Lomustine B) Axitinib	No demonstration that addition of axitinib improves results of lomustine. *mOS: 6.8 (A) vs 7.2 (B) months.*
Weathers SP [58]	2016	II	A) Bevacizumab (5mg/mq) + Lomustine B) Bevacizumab (10 mg(mq)	Bevacizumab plus Lomustine not superior to standard bevacizumab *mOS: 13.0 (A) vs 8.8 (B) months.*
Brandes AA [59]	2016	II	A) Galunisertib B) Glunisertib + Lomustine C) Lomustine + placebo	Similar clinical efficacy endpoints in all treatment arms. *mOS 8 (A), 6.7 (B), 7.5 (C) months.*
Batchelor TT [60]	2013	III	A) Cediranib B) Cediranib + Lomustine C) Lomustine	Cediranib did not improve progression free survival and other efficacy endpoints. *mOS 8 (A), 9.4 (B), 9.8 (C) months.*
Wick W [61]	2010	III	A) Enzastaurin B) Lomustine	Enzastaurin do not improved clinical outcomes over Lomustine *mOS 6.6 (A) vs 7.1 (B) months*
Field KM [62]	2015	II	A) carboplatin + bevacizumab B) bevacizumab	Addition of carboplatin did not provide additional clinical benefit. *mOS 6.9 (A) vs 7.5 (B) months*
Readon DA [63]	2012	II	A) Carboplatin irinotecan and bevacizumab	Addition of chemoterapy did not provide additional clinical benefit (compared to historically control). *mOS 8.3 months*
Aoki T [64]	2010	II	A) Ifosfamide, carboplatin and etoposide	*mOS 10.7 months*
De Groot JF [65]	2008	II	A) carboplatin + erlotinib	*mOS 7.5 months*
Brandes AA [66] AVAREG	2016	II	A) Bevacizumab B) Fotemustine	*mOS 7.3 vs 8.7 months*
Van den Bent Mj [67]	2009	II	A) erlotinib B) temozolomide/carmustine	*mOS 7.7 vs 7.3 months*
Brandes AA [68]	2009	II	A) Fotemustine	*mOS 6 months*
Friedman HS [69]	2009	II	A) Bevacizumab B) Bevacizumab + irinotecan	Addition of chemoterapy did not provide additional clinical benefit. *mOS 9.2 (A) vs 8.7 (B)*
Brandes AA [70]	2005	II	A) Carmustine + Irinotecan	*mOS 11.7 months*
Brandes AA [71]	2004	II	A) Carmustine	*mOS 7.5 months*
Reardon DA [72]	2017	III	A) Bevacizumab B) Nivolumab	Nivolumab failed to show improved OS over bevacizumab *mOS 10 (A) vs 9.8 (B) months.*
Lombardi G [73] REGOMA	2019	II	A) Regorafenib B) Lomustine	Regorafenib improved OS of patients with GBM *mOS 7.4 (A) vs 5.6 (B) months*

Table 2

Ongoing phase 3 clinical trials in recurrent glioblastoma. RT: Radiation therapy, TMZ: Temozolomide, GB: Glioblastoma, PCV: Procarbazine, lomustine and vincristine.

TRIAL	PHASE	Experimental arm		Comparator arm
NCT04277221	3	Autologous Dendritic Cell / Tumor Antigen		Bevacizumab
NCT03632135	3	Chemotherapy Guided by Cancer Stem Cell Test		Standard Chemotherapy
NCT02761070	3	Dose dense temozolomide followed by Bevacizumab		Bevacizumab
NCT02678975	2/3	Disulfiram		Alchilant chemotherapy (temozolomide, lomustine or PCV)
NCT03970447	2/3	RT+Concomitant TMZ followed by Maintenance with Regorafenib and Regorafenib for recurrent GBM		RT+Concomitant TMZ followed by Maintenance with TMZ and Lomustine for recurrent GBM
NCT03025893	3	Sunitinib		Lomustine
NCT04406272	2	VB-111 (gene therapy) before and after surgery	VB-111 (after surgery	Standard of care
NCT02394626	2	Surgery followed by adjuvant second-line		Second line alone

NCT03970447	2	RT+TMZ -> TMZ maintenance followed by lomustine at time of recurrence	RT+TMZ -> Regorafenib maintenance followed by regorafenib at time of recurrence.
NCT03743662	2	Reirradiation, bevacizumab and nivolumab in GB MGMT	Reirradiation, bevacizumab and nivolumab in GB MGMT followed by surgery.
NCT04006119	2	Ad-RTS-hIL-12 + veledimex in combination with cemiplimab-rwlc	
NCT02798406	2	Pembrolizumab plus DNX-2401	
NCT02986178	2	Polio/Rhinovirus Recombinant (PVSRIPO)	