Nonsurgical treatment of recurrent glioblastoma

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ABSTRACT

Standard treatment for glioblastoma multiforme is surgery followed by radiotherapy and chemotherapy, generally with temozolomide. However, disease recurs in almost all patients. Diagnosis of progression is complex given the possibility of pseudoprogression.

The Response Assessment in Neuro-Oncology criteria increase the sensitivity for detecting progression. Most patients will not be candidates for new surgery or re-irradiation, and anticancer drugs are the most common approach for second-line treatment, if the patient's condition allows. Antiangiogenics, inhibitors of the epidermal growth factor receptor, nitrosoureas, and re-treatment with temozolomide have been studied in the second line, but a standard therapy has not yet been established. This review considers currently available medical treatment options for patients with glioblastoma recurrence.

Key Words   Glioblastoma, chemotherapy, recurrent disease

INTRODUCTION

The annual incidence of glioblastoma multiforme (GBM) is about 3.19 cases per 100,000 population, and average age at diagnosis is 64 years[1]. Most patients with GBM survive approximately 1 year, and only 5% live for more than 5 years. Although first-line treatment has been clearly defined since 2005, no standard second-line treatment has yet been determined[2]. No prevention strategy is known, but several possible risk factors have been discussed. The use of cellphones, for example, has triggered much debate[3]. Another possible risk factor is prior exposure to radiotherapy for the treatment of disorders such as leukemia. Neurofibromatosis (types 1 and 2), Turcot syndrome, and Li–Fraumeni syndrome are also known to increase the risk of GBM.

Most treatments cannot eradicate all tumour cells, explaining the high rate of progression. Surgery is often insufficient, given the diffuse nature of the disease. Chemotherapy also has major limitations. Because most drugs cannot cross the blood–brain barrier, penetration into brain cells is limited. The great heterogeneity of the cells in brain tumours is another reason that treatments are of limited efficacy[4].

Survival in newly diagnosed patients has increased slightly, to 9.7 months in 2005–2008 [since the introduction of temozolomide (TMZ)] from 8.1 months in 2000–2003[1,2]. Standard treatment for GBM consists of maximal surgical resection followed by 6 weeks of radiotherapy (dose: 60 Gy), together with concomitant chemotherapy with TMZ (75 mg/m^2 daily). Once chemoradiotherapy is complete, a minimum of 6 months of adjuvant treatment with TMZ is started (dose: $150–200 \text{ mg/m}^2$ for 5 days every 28 days)[5].

Prognosis and response rates with TMZ are known to be better in patients presenting with a methylated *MGMT* promoter gene[5]. Survival of patients with methylated *MGMT* is 21.7 months compared with 15.3 months for patients with a non-methylated gene[6]. Recent clinical trials in elderly patients (more than 65 years of age) diagnosed with GBM showed that TMZ is not inferior to radiotherapy. Patients with *MGMT* promoter methylation experienced the best results, facilitating decision-making in this fragile elderly population[7].

The results of two phase III clinical trials—RTOG and AVAGLIO—were recently reported. Those studies investigated the addition of bevacizumab to standard treatment with TMZ. No increase in overall survival (OS) was observed, but disease-free survival increased. That finding caused considerable debate with respect to whether the combination is cost-effective in first-line treatment[8,9].

Several clinical studies have looked at the use of various drugs: for example, integrin inhibitors (cilengitide), other antiangiogenics (cediranib), and vaccines against the epidermal growth factor receptor [EGFR—specifically EGFR

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variant III (EGFRVIII), which is detected in 30% of patients]. Another innovative strategy in research is application of the NovoTTF-110A device (Novocure, St. Helier, Jersey Isle) for several hours daily. The NovoTTF-110A delivers alternating intermediate-frequency electrical fields (100–300 kHz) as an adjunct to standard treatment. Immunotherapy has not demonstrated any conclusive results to date[2].

RECURRENCE

Diagnosis

Radiologic diagnosis with magnetic resonance imaging is the reference tool for follow-up of GBM. Follow-ups are typically performed every 2–3 months. Criteria to assess progression have been established by the Response Assessment in Neuro-Oncology Working Group[10] (Tables I–III). Pseudoprogression is not uncommon in the first months after radiotherapy, having an incidence of about 20%–30% in patients who continue treatment with TMZ and radiotherapy. Pseudoprogression phenomena are the result of radionecrosis, which is characterized by disruption of the blood–brain barrier, edema, and mass effect, simulating true progression.

To date, and because of the challenges in assessing response, clinical trials in brain tumours have generally used a primary endpoint of progression-free survival [PFS (median or at 6 months)]. Progression is therefore the main endpoint for evaluating response, and in that respect, the Response Assessment in Neuro-Oncology criteria have established accurate data.

Treatment

After failure of initial treatment, therapeutic options in GBM are limited. There is no standard treatment for recurrent GBM. Progression-free survival after recurrence or progression is approximately 10 weeks, and OS is 30 weeks. Surgery, when feasible, is recommended, but no robust data supporting an increase in survival are available[11]. Repeat surgery can help to improve symptom control, confirm the diagnosis, and rule out pseudoprogression or radionecrosis. Approximately 25% of patients are considered for surgery after recurrence. A favourable prognosis has been reported in female patients less than 70 years of age with tumours of approximately 50 cm^3 and with a good performance status[12].

In certain situations, such as total resection, repeat surgery can allow for intralesional chemotherapy with carmustine wafers (Gliadel: Arbor Pharmaceuticals, Atlanta, GA, U.S.A.), an approach that can increase time to progression[4]. Gliadel wafers are implants for intracranial use that contain carmustine, a nitrosourea alkylating agent, and polifeprosan, a biodegradable copolymer that controls release of the carmustine. The wafers were approved in 2002 by the U.S. Food and Drug Administration (FDA) for newly diagnosed high-grade glioma. In 1995, Gliadel wafers had been approved by the FDA for the treatment of recurrent GBM.

A prospective randomized placebo-controlled study to evaluate the effectiveness of Gliadel wafers randomly assigned 222 patients with recurrent malignant brain

TABLE I   Determining first progression, depending on time from initial chemoradiotherapy[10]

Timing of progressive disease from completion of chemoradiotherapy	Definition
<12 Weeks after	Progression can be defined using diagnostic imaging only if new enhancement occurs outside the radiation field (beyond the high-dose region or the 80% isodose line) or if unequivocal evidence of viable tumour is obtained on histopathologic sampling (for example, >70% tumour cell nuclei in solid tumour areas, high or progressive increase in the MIB1 proliferation index compared with prior biopsy, or evidence for histologic progression or increased anaplasia in tumour). Given the difficulty of differentiating true progression from pseudoprogression, clinical decline alone—in the absence of radiographic or histologic confirmation of progression—will not be sufficient for definition of progressive disease in the first 12 weeks after completion of concurrent chemoradiotherapy.
≥12 Weeks after	1. A new contrast-enhancing lesion outside of the radiation field on declining, stable, or increasing doses of corticosteroids. 2. Increase by 25% or more in the sum of the products of the perpendicular diameters from the first post-radiotherapy imaging (or subsequent imaging showing a smaller tumour size) to the imaging at 12 weeks or later on stable or increasing doses of corticosteroids. 3. Clinical deterioration not attributable to concurrent medication or comorbid conditions is sufficient to declare progression on current treatment, but not for entry onto a clinical trial for recurrence. 4. For patients receiving antiangiogenic therapy, a significant increase in a T2 or FLAIR (fluid-attenuated inversion recovery) non-enhancing lesion can also be considered progressive disease. The increased T2 or FLAIR must have occurred compared with baseline imaging or the best response after initiation of therapy, with the patient on stable or increasing doses of corticosteroids, and must not be a result of comorbid events (for example, effects of radiation therapy, demyelination, ischemic injury, infection, seizures, postoperative changes, or other treatment effects).

TABLE II Criteria for response assessment incorporating magnetic resonance imaging and clinical factors[10]

Response	Criteria
Complete	Requires all of ■ complete disappearance of all enhancing measurable and non-measurable disease sustained for at least 4 weeks. ■ no new lesions. ■ stable or improved non-enhancing [T2 or FLAIR (fluid-attenuated inversion recovery)] lesions. ■ patient off corticosteroids (or on physiologic replacement doses only). ■ clinical stability or improvement. Patients with non-measurable disease only cannot have a complete response; the best possible response is stable disease.
Partial	Requires all of ■ 50% or greater decrease compared with baseline in the sum of the products of the perpendicular diameters of all measurable enhancing lesions sustained for at least 4 weeks. ■ no progression of non-measurable disease. ■ no new lesions. ■ stable or improved non-enhancing (T2 or FLAIR) lesions compared with baseline imaging, with patient on same or lower dose of corticosteroids. ■ a corticosteroid dose at the time of the scan evaluation that is no greater than the dose at time of baseline imaging. ■ clinical stability or improvement. Patients with non-measurable disease only cannot have a partial response; the best possible response is stable disease.
Stable disease	Requires all of ■ disqualification of complete response, partial response, or progression. ■ stability of non-enhancing (T2 or FLAIR) lesions compared with baseline imaging, with patient on the same or a lower dose of corticosteroids. In the event that the corticosteroid dose was increased for new symptoms and signs without confirmation of disease progression on neuroimaging, and that subsequent follow-up imaging shows that the increase in corticosteroids was required because of disease progression, the last imaging considered to show stable disease will be the imaging obtained when the corticosteroid dose was equivalent to the baseline dose.
Progression	Any of ■ 25% or greater increase in sum of the products of the perpendicular diameters of enhancing lesions compared with the smallest tumour measurement obtained (either at baseline, if no decrease; or at best response) on stable or increasing doses of corticosteroids[a]. ■ significant increase in T2 or FLAIR non-enhancing lesion on stable or increasing doses of corticosteroids compared with baseline scan or best response after initiation of therapy.

[a] Not caused by comorbid events (for example, radiation therapy, demyelination, ischemic injury, infection, seizures, postoperative changes, or other treatment effects); any new lesion; clear clinical deterioration not attributable to other causes apart from the tumour (for example, seizures, medication adverse effects, complications of therapy, cerebrovascular events, infection, and so on) or changes in corticosteroid dose; failure to return for evaluation as a result of death or deteriorating condition; or clear progression of non-measurable disease.

TABLE III Summary of the proposed Response Assessment in Neuro-Oncology criteria[10]

Criterion	Complete response	Partial response	Stable disease	Progressive disease
T1 Gd-enhancing disease	None	≥50% ↓	<50% ↓ but <25% ↑	≥25% ↑[a]
T2 or FLAIR	Stable or ↓	Stable or ↓	Stable or ↓	↑[a]
New lesion	None	None	None	Present[a]
Corticosteroids	None	Stable or ↓	Stable or ↓	Not applicable[b]
Clinical status	Stable or ↑	Stable or ↑	Stable or ↑	↓[a]
Requirement for response	All	All	All	Any[a]

[a] Progression occurs when this criterion is present.
[b] In the absence of persistent clinical deterioration, an increase in corticosteroids alone will not be taken into account in determining progression.
FLAIR = fluid-attenuated inversion recovery.

tumours requiring re-operation to receive surgically implanted biodegradable polymer discs with or without carmustine. Median survival was 31 weeks in the 110 patients who received carmustine polymers compared with 23 weeks in the 112 patients who received placebo wafers (hazard ratio: 0.67; p = 0.006 after accounting for the effects of prognostic factors). In patients with GBM, 6-month survival was almost 50% greater in those treated with carmustine wafers than in those treated with placebo [mortality: 47 of 73 (64%) vs. 32 of 72 (44%); p = 0.02]. No clinically important adverse reactions related to the carmustine wafers were observed, either in the brain or systemically. Interstitial chemotherapy delivered by polymer wafer directly to brain tumours at the time of surgery seems to be a safe and effective treatment for recurrent malignant glioma after repeat intervention[13].

Re-irradiation is another option to be considered, taking into account recent advances in radiotherapy techniques. The topic of re-irradiation is generally controversial because of the risk of toxicity. In fact, the high radiotherapy dose typically applied in the first line to reduce the risk of in-field relapse (about 60 Gy) generally hampers use of a second full-dose radiotherapy course. However, re-irradiation has been shown to be of value after local relapse. The literature provides consistent data supporting both the feasibility and the survival-lengthening capability of radiation compared with supportive care only. Some studies suggest a benefit for the treatment of recurrence. A published case series reported an increase in os of 79% at 6 months and 30% at 1 year with re-irradiation. Re-irradiation can be considered in selected patients with a Karnofsky performance status above 60%, a major lesion size below 40 mm, and progression more than 6 months after surgery. The dose most frequently reported, with or without modulated intensity, falls in the range of 30–60 Gy[14].

Multiple chemotherapy options are available for second-line treatment, but no standard of care has been established. Results reported so far have been generally discouraging in terms of os; furthermore, the impact of the treatments on quality of life in patients is difficult to evaluate.

The next few sections describe the most relevant trials performed to date with respect to the medical treatment of recurrent GBM. It must be emphasized that certain patients will be candidates only for symptomatic treatment because of poor general condition or comorbidities. Ensuring appropriate management and support for the complications that typically occur during the course of the disease (convulsions, thrombosis, and cognitive deterioration) is essential.

NITROSOUREAS AND ALKYLATING AGENTS IN MONOTHERAPY

Nitrosoureas are alkylating agents characterized by high lipophilicity, allowing them to cross the blood–brain barrier. The first drugs of this type to be used in the treatment of GBM were carmustine, lomustine, and nimustine. Procarbazine has also been used in monotherapy and in combination with lomustine. The main toxicities of these agents are renal, hepatic, and pulmonary (fibrosis).

In 1999, TMZ was described as beneficial for patients with recurrent GBM before treatment with nitrosoureas[15]. Because TMZ's tolerability as second-line treatment was good, it was later studied in the first line, with Stupp et al.[5] showing in 2005 that TMZ in combination with radiotherapy was the most effective schedule for GBM treatment to that date. Temozolomide is now the accepted standard for first-line treatment. Nimustine in monotherapy in pre-treated patients or in combination with teniposide or cytarabine has yielded a 6-month PFS (PFS-6) of 20%, with a median os of 6.7 months[16].

Two phase II clinical trials[17,18] and a retrospective study[19] assessed the efficacy of carmustine monotherapy in recurrent GBM. The reported PFS-6 was in the range 13.0%–17.5%, and median os ranged from 5.1 months to 7.5 months.

A phase III clinical trial[20] evaluated enzastaurin using lomustine as a control (92 patients, 70 at first recurrence), finding a PFS-6 of 19% and a global median os of 7.1 months. Grade 3 and 4 hematologic toxicity was frequent (50% of patients), and the efficacy of enzastaurin in recurrent GBM was determined to be negative.

The nitrosourea fotemustine has been investigated mainly in Italy and France. Several phase II studies using various schedules of the drug have been published, showing a PFS-6 in the range of 20.9%–61% and a median os of 6–11 months. The best toxicity profile was found with use of the schedule set out by Addeo et al.[21]. Phase III studies are needed to ascertain the value of their encouraging schedule in second-line treatment.

Several studies have assessed TMZ as monotherapy, but few were prospective or randomized. Some studies have evaluated extended-dose TMZ schemes so as to increase depletion of O^6-alkylguanine DNA alkyltransferase (MGMT). Other studies have compared the TMZ monotherapy schedules with the standard TMZ schedule (150–200 mg/m^2 for 5 days every 4 weeks)[22–24]. Results with extended metronomic TMZ schedules of 75–100 mg/m^2 daily have also been reported[25–29]. A phase II clinical trial (Wick et al.[30]) assessed a TMZ schedule of 7 days on and 7 days off treatment, resulting in modest efficacy without a relevant increase in toxicity. The authors reported a response rate of 10%, a PFS-6 of 48%, and a median time to progression of 21 weeks. In the foregoing clinical trials, half the patients had received prior chemotherapy, mainly nitrosoureas. A total of 372 patients had not received prior TMZ. Reported values for PFS-6 ranged between 18% and 48%, and median os was in the range 5.4–9.9 months.

In recent years, several clinical trials in patients treated with TMZ in the first and second line have been reported. The second-line schedules ranged from 7 days on and 7 days off to 21 days on and 7 days off, and reported PFS-6 values in the range 26%–58.3% and median os durations of 5.1–13 months, depending on the study[25–29]. Relevantly, Perry et al.[28] analyzed the efficiency of TMZ in second-line treatment based on time to first progression. Patients defined as early TMZ (progression while receiving adjuvant TMZ and before completion of 6 cycles) had a PFS-6 of 27% and a median os of 3.6 months. For patients with progression after receiving 6 cycles of adjuvant TMZ, PFS-6 was 7.4%, and median os was 1.8 months. Nevertheless, those who started taking

TMZ again after a treatment-free interval experienced a PFS-6 of 35.7% and a median OS of 3.7 months. The authors pointed to pseudoprogression as a possible explanation for the unbalanced results. The average survival time from completion of radiotherapy was 5.2 months, which indeed minimizes the effect of pseudoprogression.

Other studies have compared TMZ with other drugs. In a comparison with procarbazine[31], the PFS-6 was 21% for TMZ and 8% for procarbazine, with a median OS in the TMZ arm that was longer by 1.5 months. The DIRECTOR trial evaluated two regimens of dose-dense TMZ (120 mg/m^2 daily 1 week on and 1 week off vs. 80 mg/m^2 daily 3 weeks on and 1 week off) in patients after first recurrence and after at least 2 cycles of TMZ[32]. The main toxicities after the reintroduction of TMZ in second-line treatment were grades 3 and 4 hematologic events. Wick *et al.*[30] reported that the safety profile of the various dose-dense TMZ schedules is similar to those of the classic 5-day schedule, the main difference being an increase in lymphopenia. However, no clear evidence of cumulative toxicity has emerged. It can be concluded from all these studies that no clear evidence suggests superiority for the metronomic schedules over the standard TMZ schedule.

Patients with methylated *MGMT* experience better results in terms of PFS and OS after second-line treatment with alkylating drugs. Compared with patients having a non-methylated gene, such patients also have a higher probability of achieving a radiologic response. A patient's *MGMT* methylation status can change with the clinical evolution of GBM; however, a clinical trial in 80 patients with recurrent GBM found that *MGMT* status changed in only 11.2% of patients, indicating that a re-evaluation of *MGMT* status is not necessary when patients progress.

COMBINATIONS WITH ALKYLATING AGENTS

A combination of procarbazine, lomustine, and vincristine resulted in a PFS-6 of 30%–38% and a median OS of 7.6–7.9 months, with grade 3 or 4 hematologic toxicity of 26%[33]. In a phase III clinical trial, Bachelor *et al.*[34] assessed the value of an angiogenesis inhibitor in 325 patients. The three arms of the trial were allocated 2:2:1 to cediranib 30 mg monotherapy, cediranib 20 mg plus lomustine 110 mg/m^2, and lomustine 110 mg/m^2 plus placebo respectively. The primary endpoint was PFS-6, and no significant differences between the arms were observed. In 129 patients, lomustine in combination with cediranib resulted in a PFS-6 of 34.5% and an OS of 9.4 months, similar to results with lomustine monotherapy, but with major hematologic toxicity for the combination. In a study by Gaviani *et al.*[35] evaluating the combination of TMZ and fotemustine in 10 patients, major hematologic toxicity invalidated the combination. A combination of daily TMZ (50 mg/m^2) and sorafenib showed only modest efficacy (1 response in 32 patients) and a very low PFS-6 of 9.4%[36].

A retrospective study in 28 patients tested a combination of TMZ (10 mg/m^2 twice daily) and celecoxib (200 mg daily), achieving a PFS-6 of 43%[37]. Of the 28 patients, 68% underwent surgical resection before treatment. The main toxicity in the study was lymphopenia. Temozolomide in combination with O^6-benzylguanine (an agent that induces MGMT depletion) was studied in 34 patients[38]. The PFS-6 achieved in that study was modest (9%), with a median OS of 4.5 months.

Combinations do not appear to add any benefit to TMZ alone.

TREATMENT WITH ANTIANGIOGENICS

Antiangiogenics have been very promising agents for the second-line treatment of recurrent GBM.

Bevacizumab is a monoclonal antibody with activity against the vascular endothelial growth factor (VEGF). It was approved by the FDA in 2009 for the treatment of the GBM on the basis of two phase II clinical trials that, in comparisons with historical controls, showed high response rates and superior duration of response. By contrast, the European Medicines Agency has not approved bevacizumab because of the lack of a comparison against a control drug. Three phase II clinical trials and a retrospective study evaluated bevacizumab monotherapy in patients pretreated with TMZ after progressive disease[39–42]. Bevacizumab was dosed intravenously at 10 mg/kg every 2 weeks in two of the studies and at 15 mg/kg every 3 weeks in the third[41]. In those studies, the PFS-6 ranged from 25% to 42.6%, and the OS, from 6.5 months to 9.2 months. The radiologic response in the studies was very encouraging, with 62 of 183 patients achieving a response (33.9%). The most frequent grades 3 and 4 toxicities were hypertension, thromboembolic events, and fatigue.

Available data have not shown that monotherapy is better than combination treatment. Bevacizumab has been used in combination with irinotecan, carboplatin, etoposide, and TMZ. The best results so far have been achieved in combination with irinotecan. Irinotecan was dosed at 125 mg/m^2 every 2 weeks or at 340 mg/m^2 if patients were receiving anti-epileptics. The reported PFS-6 ranged from 30.0% to 50.3%, and the OS, from 6.1 months to 9.7 months[43]. One of the most controversial issues in the use of bevacizumab is duration of treatment. Most patients are treated until progression—that is, for an average of 4–6 months. Bevacizumab has an anti-edema effect that allows for a decrease in the administration of corticosteroids, with a consistent minimization of the related side effects. However, interruption of bevacizumab is associated with a rebound effect, and some authors consider that extending treatment until progression increases OS.

A phase II trial studied a triple-therapy approach using bevacizumab, irinotecan, and cetuximab[44]. The response rate was 34%, the PFS-6 was 33%, and the OS was 7 months. Another triple combination tested was bevacizumab, carboplatin, and etoposide[45]; results were similar to those in other studies (PFS-6: 22%; OS: 6.9 months). Reardon *et al.*[46] evaluated the efficacy of bevacizumab and etoposide in 27 patients, reporting a PFS-6 of 44.4% and a median OS of 10.2 months. Patients with high overexpression of VEGF (30% of the cohort) experienced better PFS.

Sathornsumetee *et al.*[47] evaluated bevacizumab in combination with erlotinib in a phase II trial in 24 patients who had received prior TMZ. Those authors reported a PFS-6 of 29% and an OS of 10.3 months, results that are similar to those achieved with bevacizumab monotherapy.

In BELOB, another recently reported open-label randomized controlled study, 148 eligible patients were randomly assigned to one of three treatment arms: 10 mg/kg bevacizumab every 2 weeks until progression, plus 110 mg/m^2 lomustine every 6 weeks for 6 cycles (52 patients); 10 mg/kg bevacizumab every 2 weeks until progression (50 patients); or 110 mg/m^2 lomustine every 6 weeks for 6 cycles (46 patients). At 9 months, the os rates were 59% [95% confidence interval (CI): 43% to 72%] in the combination arm with the lower dose of lomustine; 43% (95% CI: 29% to 57%) in the single-agent lomustine arm; and 38% (95% CI: 25% to 51%) in the single-agent bevacizumab arm. The PFS-6 rate, a secondary endpoint of the trial, also favoured the combination arm at 41%, compared with 13% in the single-agent lomustine arm and 16% in the single-agent bevacizumab arm. Median survival was 11 months in the combination arm compared with 8 months in the other two arms. A phase III trial comparing a combination of bevacizumab and lomustine with single-agent lomustine for the treatment of recurrent GBM is ongoing[48].

A multicentre open-label randomized (2:1) phase II trial has since been published (AVAREG study). The regimen in that study was bevacizumab 10 mg/kg every 2 weeks, or fotemustine 75 mg/m^2 on days 1, 8, and 15 followed (after a 34-day interval) by fotemustine 100 mg/m^2 every 3 weeks. The primary endpoint was os at 6 months. The bevacizumab arm enrolled 59 patients with recurrent GBM; the fotemustine arm enrolled 21. The 6-month os was 62.1% in patients treated with bevacizumab and 73.3% in patients treated with fotemustine. The 9-month os was 37.9% and 46.7% in the bevacizumab and fotemustine arms respectively. Median os was 7.3 months (95% CI: 5.8 to 9.2 months) in the bevacizumab arm and 8.7 months in the fotemustine arm[49].

Other antiangiogenic drugs have also been tested. As mentioned earlier, results of a phase III clinical trial with cediranib were negative. Another antiangiogenic agent that has been tested is aflibercept[50]. In 42 patients at first recurrence, assessment of single-agent aflibercept showed minor efficacy (PFS-6: 7.7%). The most frequently reported grade 3 toxicities were asthenia and hypertension. Also tested recently was the Met, VEGFR2, and Ret inhibitor called XL184 (cabozantinib). Studied at doses of 125 mg or 175 mg daily in 124 patients with recurrent GBM[51], it resulted in PFS-6 rates of 25% (125 mg dose) and 21% (175 mg dose). Toxicities reported were fatigue (23%), hypophosphatemia (10%), increased lipases (10%), migraine, lymphopenia, and convulsion (9%).

Treatment for GBM, the most common primary malignant brain tumour in adults, remains a significant unmet need in oncology. Historically, cytotoxic treatments provided little durable benefit, and tumours recurred within several months, spurring a substantial research effort to establish more effective therapies for both newly diagnosed and recurrent GBM. In that context, antiangiogenic therapy emerged as a promising treatment strategy because GBM is a highly vascular tumour. In particular, GBM overexpresses VEGF, a pro-angiogenic cytokine. Many studies have demonstrated promising radiographic response rates, delayed tumour progression, and a relatively safe profile for anti-VEGF agents. However, randomized

phase III trials conducted to date have failed to show an os benefit for antiangiogenic agents alone or in combination with chemoradiotherapy. Those results indicate that antiangiogenic agents might not be beneficial in unselected populations of patients with GBM. Unfortunately, biomarker identification has lagged behind the process of drug development, and no validated biomarker for patient stratification exists. However, hypothesis-generating data from phase II trials that reveal an association between increased perfusion or oxygenation (that is, the consequences of vascular normalization) and survival suggest that early-imaging biomarkers could help to identify the subset of patients who will most likely benefit from anti-VEGF agents.

INHIBITORS OF EGFR: MONOTHERAPY OR COMBINATION?

The response to inhibition of EGFR in GBM has been studied with inconclusive results. The first study, by Ritch et al.[52], tested gefitinib, but obtained no responses. Studies by Mellinghoff et al.[53] and Haas-Kogan et al.[54] reported encouraging results. Mellinghoff et al. concluded that co-expression of EGFRVIII with preservation of PTEN determined by immunohistochemistry was associated with a high response rate (about 50%) to EGFR inhibition. In a series of 41 patients, Haas-Kogan et al. reported observing 8 responses in individuals who expressed high levels of EGFR and low levels of Akt. A recent prospective study of erlotinib[55] did not reproduce the latter findings. Conducted in patients with recurrent GBM and with co-expression of EGFRVIII and PTEN determined by immunohistochemistry, that study reported an os of 7 months and a PFS of 3 months.

In most trials in recurrent patients treated with EGFR inhibitors, results were negative. A phase II clinical trial by the European Organisation for Research and Treatment of Cancer randomized 110 patients to treatment with erlotinib ($n = 54$) or to chemotherapy with TMZ or carmustine ($n = 56$). The PFS-6 was 12% in patients treated with erlotinib and 24% in patients receiving control chemotherapy, with similar survival in both arms. Response was worse in the 13 patients with EGFRVIII mutations. The authors concluded that response to erlotinib does not correlate with EGFR or EGFRVIII[17]. Yung et al.[56] treated 48 patients with erlotinib and reported a response rate of 6.3%, an os of 7 months, and a PFS of 3 months. Amplification of EGFR was not related to an increase in response. Raizer et al.[57] published similar results after treating 53 GBM patients with erlotinib. In their study, PFS was 2 months. Those disappointing results moved some investigators to assess different combinations. Nguyen et al.[58] reported on 19 patients treated with everolimus and gefitinib in a phase I/II clinical trial; their PFS was 2.6 months, similar to that achieved with monotherapy. Doherty et al.[59] assessed 28 patients who were treated with EGFR inhibitors (erlotinib, gefitinib) in combination with sirolimus, an inhibitor of mTOR (mammalian target of rapamycin). Those authors found that 19% of patients achieved a partial response and 50% experienced stable disease. The PFS-6 was 25%. A phase II study by De Groot et al.[60] used a combination of carboplatin and erlotinib in patients with recurrence. Of 43 assessable patients, 1 achieved

a partial response; another 20 patients (47%) experienced stable disease for an average of 12 weeks. Median PFS duration was 9 weeks, and the PFS-6 rate was 14%. Median OS was 30 weeks. The carboplatin–erlotinib regimen was well tolerated, with some patients experiencing grade 3 and 4 toxicities of fatigue, leucopenia, thrombocytopenia, and rash that required dose reductions.

The combination of TMZ with afatinib (40 mg daily), an irreversible inhibitor of mutated EGFR, achieved good results. The PFS-6 for combination therapy was 10%; it was 3% for afatinib monotherapy. The main grade 3 toxicities were diarrhea and skin toxicity[61].

Little is known about the pharmacokinetics of erlotinib. After treatment with erlotinib at the usual dose of 150 mg, the average levels of erlotinib and OSI-420 (a metabolite) in cerebrospinal fluid were 54 ± 30 ng/mL and 10.8 ± 8.2 ng/mL respectively. The average percentage of the dose that reached the cerebrospinal fluid was $5.1\% \pm 1.9\%$ for erlotinib and $5.8\% \pm 3.6\%$ for OSI-420. Those discouraging results[62,63] probably explain why the usual dose is inadequate in the clinical setting. Vivanco et al.[64] showed that the most frequent mutation of *EGFR* in GBM is relatively insensitive to erlotinib, being more sensitive to other EGFR inhibitors (for example, HKI-272 or lapatinib).

IMMUNOTHERAPY

Phase I and II trials have studied the immunotherapeutic approach in GBM, with encouraging results. Phase III trials with anti-EGFR vaccines are currently underway, but results are not yet available.

An excellent review of all the trials of immunotherapy in GBM suggests that vaccination is safe in terms of side effects and effectivity[65]. Trials of adjuvant therapy using autologous loaded dendritic cells and antigen-presenting cells have reported PFS and OS increases in patients on first-line treatment and with recurrent GBM.

Immunotherapy using dendritic cell vaccination in recurrent GBM has been assessed in twelve studies (including four with a control arm). In seven of the studies, the immunotherapy arm experienced better results in terms of OS. In ten of the studies, median OS ranged from 38 weeks to 138 weeks. As cited in Bregy et al.[66], the best results for median OS were reported by Chang et al. (138 weeks), Yu et al. (133 weeks), and Yamanaka et al. (111 weeks). Those three studies had in common vaccination given immediately after surgery.

OTHER AGENTS

A great number of agents, especially those that act on specific molecular targets, have been evaluated in the treatment of recurrent GBM.

Cilengitide is an inhibitor of integrin αVβ3 and αVβ5. In a clinical trial involving 40 patients, cilengitide showed minor toxicity and modest activity in monotherapy, with a PFS-6 of 15% and a global survival of 9.9 months at a dose of 2000 mg twice daily[67]. Another study involving 26 patients found a PFS-6 of 12%.

Inhibitors of EGFR and platelet-derived growth factor receptor have been investigated, as have agents that modulate transduction routes, directly disabling MTOR, phosphoinositide 3-kinase, histone deacetylase, and farnesyltransferase—although with discouraging results[4].

A novel approach to the treatment of recurrence has been the use of intermediate-frequency electrical fields (NovoTTF-100A). Results in the treatment of GBM were reported by Stupp et al.[68] in 2012. Those authors reported efficacy similar to the modest results reached with various schedules of second-line chemotherapy. A late-breaking abstract on NovoTTF-100A presented at the 2014 Society for Neuro-Oncology conference showed statistically significant PFS and OS advantages in first-line therapy[69]. Specifically, of 700 patients enrolled in the EF-14 trial, the first 315 were analyzed, with the authors indicating that, compared with TMZ alone, treatment with the NovoTTF-100A plus TMZ was associated with an improvement in PFS (median: 7.1 months vs. 4.0 months; hazard ratio: 0.63; $p = 0.001$). Overall survival was also extended with use of the NovoTTF-100A (median: 19.6 months vs. 16.6 months with TMZ alone, for a gain of 3 months; hazard ratio: 0.75; $p = 0.034$). Those findings could potentially change the first-line therapy standard; however, treatment in the second line will continue to lack a clear option.

SUMMARY

Over recent years, multiple drugs have been assessed for the treatment of recurrent GBM, in monotherapy and in combination. The most recent studies have included mainly patients treated with first-line TMZ. Most trials lack a control arm. The primary endpoints reported are PFS-6 and OS. Response assessment in the trials is a highly controversial issue, because some experts claim that the use of the Response Assessment in Neuro-Oncology criteria are more accurate and convenient than the classical Macdonald criteria. Whichever method of assessment is used, ruling out pseudoprogression is not easy.

Most trials have reported only modest increases in PFS and minimal or even doubtful increases in OS. In the assessment of new drugs, OS is the most relevant endpoint, although results can be influenced by many events, such as repeat surgery.

In conclusion, in present-day practice, treatment of recurrent GBM should be individualized according to performance status, age, tumour histology, biomarkers, the possibility for repeat surgery, time to recurrence, and response to prior treatment. Enrolment of patients into well-designed clinical trials is recommended to advance knowledge of the disease and to maximize clinical benefit for patients.

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