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REVIEW

Recurrent Glioblastoma: Ongoing Clinical Challenges and Future Prospects

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Abstract: Virtually all glioblastomas treated in the first-line setting will recur in a short period of time, and the search for alternative effective treatments has so far been unsuccessful. Various obstacles remain unresolved, and no effective salvage therapy for recurrent glioblastoma can be envisaged in the short term. One of the main impediments to progress is the low incidence of the disease itself in comparison with other pathologies, which will be made even lower by the recent WHO classification of gliomas, which includes molecular alterations. This new classification helps refine patient prognosis but does not clarify the most appropriate treatment. Other impediments are related to clinical trials: glioblastoma patients are often excluded from trials due to their advanced age and limiting neurological symptoms; there is also the question of how best to measure treatment efficacy, which conditions the design of trials and can affect the acceptance of results by oncologists and medicine agencies. Other obstacles are related to the drugs themselves: most treatments cannot cross the blood-brain-barrier or the brain-to-tumor barrier to reach therapeutic drug levels in the tumor without producing toxicity; the drugs under study may have adverse metabolic interactions with those required for symptom control; identifying the target of the drug can be a complex issue. Additionally, the optimal method of treatment – local vs systemic therapy, the choice of chemotherapy, irradiation, targeted therapy, immunotherapy, or a combination thereof – is not yet clear in glioblastoma in comparison with other cancers. Finally, in addition to curing or stabilizing the disease, glioblastoma therapy should aim at maintaining the neurological status of the patients to enable them to return to their previous lifestyle. Here we review currently available treatments, obstacles in the search for new treatments, and novel lines of research that show promise for the future.

Keywords: glioblastoma, research, challenges, endpoints, recurrent, treatment

Introduction

The incidence of malignant tumors of the central nervous system (CNS) is 7.08 per 100,000 inhabitants in the USA. Glioblastoma (GB) accounts for 47.7% of all CNS malignant tumors in adults, and patients have a median overall survival (OS) of only eight months and a 5-year survival of 5.8% (95% CI 5.5–6.1).[1] The incidence of GB is low compared to that of other tumors, but there is no localized and surgically curable form of GB as there is in other cancers, so all cases are considered grade 4.

The standard first-line treatment for GB was established in 2005 as maximal safe surgery followed by radiotherapy plus concomitant and adjuvant temozolomide.[2] In the USA, tumor-treating fields can also be administered after chemoradiotherapy. This system delivers low-intensity, intermediate-frequency alternating fields via transducer arrays when applied to the scalp, exerting an antimitotic effect.[3] Unfortunately, only around 44–50% of patients are able to receive the full standard treatment,[4,5] only one fourth of those who start treatment are able to complete the six cycles of adjuvant temozolomide,[5] and only 60% of these patients receive second-line treatments. Fewer than 43% of GB patients are fit enough to be included in clinical trials.[6]

The symptoms of GB and the sequelae of treatments often lead to functional dependence and cognitive impairment,[7] making it impossible for patients to return to their normal pre-diagnosis activities and impacting negatively on family life. There is thus great concern about patient quality of life during the extra period of survival conferred by treatment,

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especially on the maintenance of neurocognition and the adjustment of palliative and supporting treatments, including rehabilitation.[8,9]

To date, the search for alternative effective treatments for GB has been unsuccessful. Here we review the standard of care and available therapies, obstacles in the search for new treatments, and new lines of treatment under investigation.

Currently Approved Treatments for Recurrent Glioblastoma

Several treatments have shown some efficacy in specific patients at recurrence, including second surgery (S-S), re-irradiation, and re-treatment with temozolomide, nitrosoureas or bevacizumab (Figure 1).

Patients who benefit from S-S are those with a localized relapse in non-eloquent areas, in whom a complete or subtotal resection of the enhancing tumor can be performed. Candidates for S-S need to have a good performance status and a relatively indolent tumor history, measured as a prudential time from the first to the S-S.[10–14] In general, only 20–30% of relapsed patients are eligible for S-S. Median OS after S-S is highly variable (11–17 months).[12,15] In fact, the potential benefit of S-S has never been explored in a randomized study suggesting that the increased survival attributed to S-S may be due to bias in patient selection. Consensus guidelines to select candidates for S-S have been proposed by some authors,[16] but there is no consensus on the administration of postoperative treatments after the procedure.

Re-irradiation could also be an option in selected patients, but again there is a lack of randomized studies. Several questions are unresolved, such as the criteria for selection of candidates, the type of recurrence that can be treated, the total dose, optimal fractionation and best volume.[17] The different irradiation techniques include stereotactic radiosurgery, hypofractionated stereotactic radiotherapy, and conventionally fractionated external radiotherapy. Estimated OS and progression-free survival (PFS) from re-irradiation are 73% and 43%, respectively, at six months and 36% and 17%, respectively, at 12 months.[18] Several ongoing prospective studies are testing the value of re-irradiation – either alone or in combination with systemic treatments. The main risks of re-irradiation are radionecrosis, which seems to be reduced by bevacizumab,[19] and a limited tolerance to irradiation of several areas, such as the brainstem, chiasm and optic nerves. A validated scale[20] has been published that can be useful when deciding on the use of re-irradiation in the clinical setting. Advances in technology have also led to new strategies, including proton therapy, intraoperative radiation therapy, and brachytherapy.[17]

Commonly used systemic treatments include chemotherapy with temozolomide or nitrosoureas and antiangiogenic therapy with bevacizumab. Other treatments, such as regorafenib and tumor-treating fields,[3,21] have been approved in a few countries.

Temozolomide efficacy was demonstrated in early trials,[22,23] where 6-month PFS was 21%, which was superior to other agents used at that time. When temozolomide became part of the standard first-line treatment, however, there was

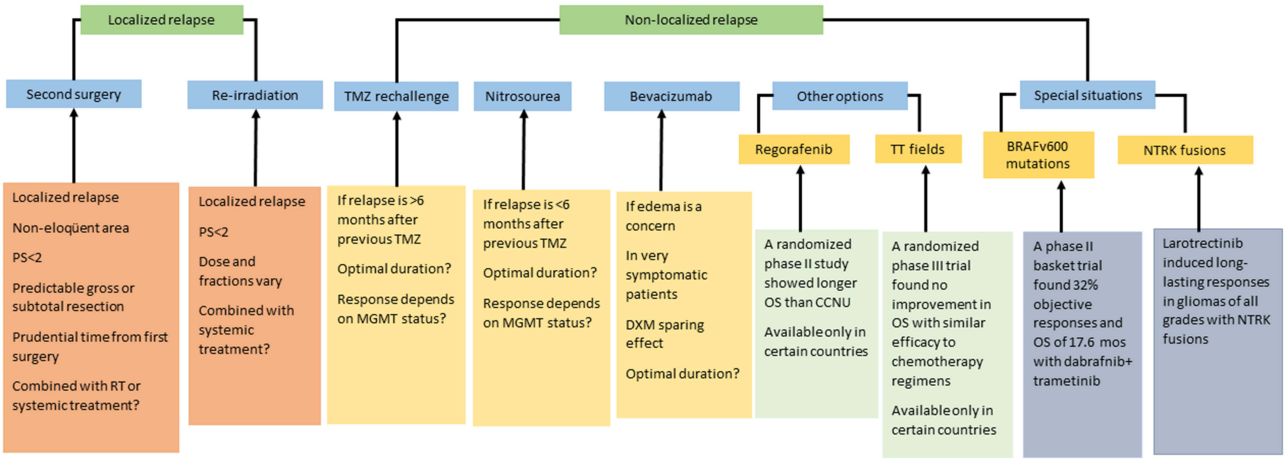

Figure 1 Treatment options for recurrent glioblastoma. Inclusion in a clinical trial is always the preferred option.

no place for its use in recurrent GB, although a rechallenge seemed to benefit some patients, especially those with the longest interval after their last cycle of standard treatment, who attained a 6-month PFS of 35.7%.[24]

Nitrosoureas, including lomustine, and procarbazine, were widely used before the availability of temozolomide, but their use is now limited to recurrent GB. Because of their liposolubility, they are able to cross the blood-brain barrier (BBB). Lomustine has become the standard of care at relapse in Europe and is the treatment in the control arm of most trials.[25] However, its benefit is limited: objective response rate around 10%; median PFS <2 months; 6-month PFS 20%; and OS 6–9 months. Thrombocytopenia is the most frequent limiting toxicity.[26] Procarbazine was found to be less effective than temozolomide in a randomized trial.[22] Fotemustine, a third-generation intravenous nitrosourea with lower rates of thrombocytopenia,[27,28] is used in several countries at different schedules.

Bevacizumab created a great expectation after the first reports showing a high objective response rate even when combined with an inactive drug in gliomas like irinotecan. This led to an accelerated US FDA approval for the treatment of recurrent GB.[29,30] Several later randomized studies in both the first-line (standard therapy with or without temozolomide)[31,32] and second-line settings (lomustine versus lomustine-plus-bevacizumab)[33] found that the addition of bevacizumab did not improve OS but did increase PFS and decreased the need for corticosteroids to treat cerebral edema. The efficacy of bevacizumab has been questioned precisely because of its antiangiogenic effect, which decreases contrast uptake on magnetic resonance imaging (MRI) but does not prevent tumor infiltration of normal brain tissue. This situation has led to different decisions by national health authorities and irregular availability around the world. A randomized trial comparing lomustine alone versus bevacizumab-plus-lomustine reported objective responses of 41.5% and median PFS of 3.8 months for the bevacizumab group, compared to 13.9% and 1.5 months with lomustine alone.[34]

Regorafenib is a multikinase inhibitor that blocks tyrosine kinases that are active in angiogenesis (VEGFR-1, VEGFR-2, VEGFR-3 and TIE2), cancer development and growth (KIT, RET, RAF1, BRAF and BFRAFV600E), and maintenance of the tumor microenvironment (PDGFR and FGFR). As some of these genes are altered in GB, there was a rationale for exploring the activity of this drug. The REGOMA trial was a Phase II randomized study comparing regorafenib and lomustine in 124 patients. There was a benefit in OS for the patients treated with regorafenib (HR 0.50; P=0.0009) although median OS was only 7.4 months in the regorafenib arm and 5.6 months in the lomustine arm.[35] Based on these findings, regorafenib was approved for treatment of recurrent GB in Italy and is included as an alternative treatment in the NCCN guidelines (https://www.nccn.org/professionals/physician_gls/pdf/cns.pdf). It is currently being tested in the phase II/III Adaptive, Global, Innovative Learning Environment (AGILE) trial (ClinicalTrials.gov NCT03970447).

In addition, alternating tumor-treating fields yielded similar outcomes to other treatments, which led to US FDA approval for recurrent GB patients.[36]

Special Patient Populations

Glioblastoma patients are often included in clinical trials of agents targeting tumor-agnostic biomarkers. Glioblastoma tumors may have alterations of BRAF (v-Raf murine sarcoma viral oncogene homolog B1) in 9% of cases. Drugs targeting BRAF v600 mutations, such as dabrafenib, vemurafenib and encorafenib, combined with MEK1/2 kinase inhibitors (as used in melanoma) have proven to be beneficial in other gliomas, including pilocytic astrocytoma and pediatric diffuse gliomas. In GBs and relapsed high-grade gliomas, the combination of dabrafenib plus trametinib attained substantially superior results to other commonly used treatments: 32% objective responses; 19% stable disease by independent radiology review; median duration of response 13.6 months; median PFS of 4.5 months; OS 17.6 months.[37] Other BRAF and MET1/2 kinase inhibitors are currently being studied in gliomas with BRAF v600 mutations (CliinicalTrials.gov NCT03973918).

Some GBs may harbor *NTRK* alterations (*NTRK1, NTRK2*, and *NTRK3*), which encode the tyrosine receptor kinases TRK-A, TRK-B, and TRK-C, respectively. The most clinically relevant alterations are *NTRK* fusions, which lead to constitutively activated receptors or splice variants, mutations, copy number alterations and increased expression with oncogenic potential. Targetable fusions are rare in adult GB (1.7%).[38] *NTRK* fusions are druggable with entrectinib or larotrectinib, both of which can cross the BBB.[39] Entrectinib is a selective tyrosine kinase inhibitor of TRK-A, TRK-B

and TRK-C, the proto-oncogene ROS1, and ALK. It induced 55% of objective responses in patients with brain metastases from non-CNS tumors.[40] Larotrectinib, a TRK inhibitor, induced 30% of responses in gliomas of all grades harboring TRK fusions, including in adult patients (7 of 33). The 24-week disease control rate was 73% and 1-year PFS was 56%.[41] Larotrectinib was approved by the US FDA based on overall response rate and duration of response while awaiting results of confirmatory trials.

FGFR alterations, such as gene amplification, overexpression, mutations (FGFR 1–4) and fusions (*FGFR:TACC3*) are found in 8% of high-grade gliomas.[38,42] Several inhibitors targeting these alterations are being studied. An interim analysis of the basket trial RAGNAR reported 20.7% of responses in 29 heavily pre-treated patients with high-grade gliomas treated with erdafitinib.[43] Infigratinib has been tested in a phase II trial and while the response rate was not outstanding, several patients had long-lasting responses.[44] Although these are very initial results, it seems that this pathway of inhibition will continue to develop in the near future. Pending concerns are the identification of the alteration with the best response to therapy and of the agent most capable of crossing the BBB.[45]

Novel Lines of Research in Glioblastoma and Gliomas in General

Research in glioblastoma encompasses not only treatment therapy but also improvements in imaging technology, the application of artificial intelligence to radiogenomics, surgical technology advances, which in turn impact on irradiation treatment technique, and other advances such as molecular sequencing, liquid biopsy and better GB models for pre-clinical research as 3D organoid -based GB model systems among others. In addition to research into how to measure the impact of treatments on patients, their quality of life and patient reported outcomes. All of these are moving forward intertwined in an interconnected network. In the present review we will focus on the specific treatment of the disease. Figure 2 shows some of the focuses of current GB research.

Overcoming the BBB

One line of research has focused on disrupting the BBB/BTB to facilitate the extravasation of drugs into the brain parenchyma. This can potentially be achieved with hyperosmolar agents like mannitol or focused ultrasounds

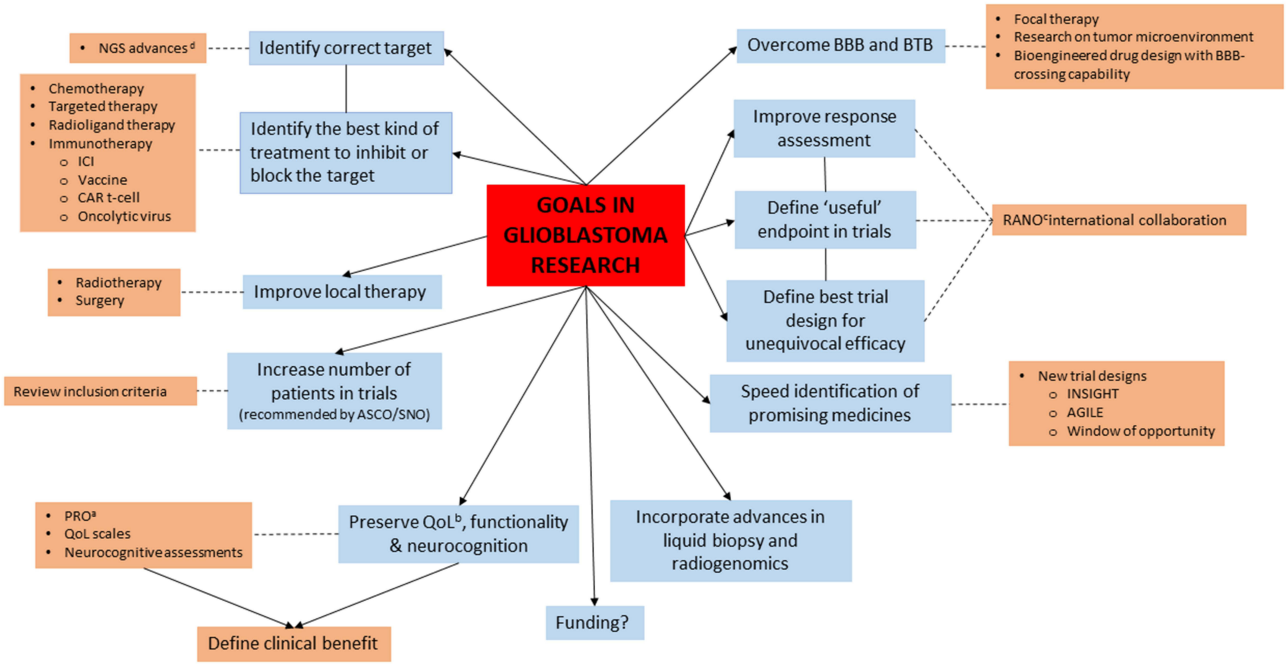

Figure 2 Goals of glioblastoma research and the means by which they can be achieved. [a]Patient reported outcomes, [b]Quality of life, [c]Response assessment in Neuro-oncology, [d]Next generation sequencing.

(ClinicalTrials.gov NCT04614493), which induce vasodilation and shrinkage of endothelial cells, thus opening the tight junctions and increasing the permeability of the BBB.[46–49]

Other research has focused on the use of lipid carriers, prodrugs, stem cells, exosomes, gene therapy, biologics or nanoparticles.[50] Nanomedicine structures of 10–500-nm particles can be built with different core materials, such as polymers, lipids, dendrimers or inorganic materials, and can be loaded with different drugs and administered locally or systemically by different routes. Over the last years, a large amount of research has explored this technology, which is leading to improved solubility, stability, biodistribution, release kinetics, biocompatibility, tumor accumulation and a good toxicity profile.[51–53] Early-phase trials are ongoing.[54] However, the complex and heterogeneous nature of GB requires these technologies to be tested on advanced models of the disease, such as patient-derived organoids or xenografts, before considering translation to the clinic.

Another line of research is re-engineering biologics to enable them to cross the BBB with molecular Trojan horse technology using a monoclonal antibody against an endogenous BBB receptor transporter[55] or designing bioengineered drugs with a high a priori ability to cross the BBB, as is the case of the ATM kinase inhibitor AZD1390.[56]

Local Therapy

Local therapy could potentially avoid the BBB and systemic toxicity and attain high concentration levels near the tumor, but it would only be beneficial in localized relapses. Different materials have been studied, including wafers, hydrogel depots, microparticles and fibers, and foam formulations loaded with different drugs or biologics that do not reach therapeutic concentrations after systemic administration or even direct instillation into the tumor mass by convection enhanced delivery. Only Gliadel®, an implantable intracavitary wafer loaded with carmustine, has shown benefit in randomized studies in the recurrent setting.[57] Potential complications, including cerebral edema, intracranial hypertension, CSF leakage, and seizures, have prevented the standardization of this treatment.[3,21] Research continues in this context and studies in newly diagnosed patients are ongoing (ClinicalTrials.gov NCT03657576, NCT03152318, NCT04135807).[58]

Chemotherapy

Chemotherapy seems to have been dropped from the therapeutic arsenal for GB, probably because current research is focusing on new treatment modalities like immunotherapy and targeted therapy. Nonetheless, several agents are being evaluated, including lisavanbulin (BAL101553), a microtubule-targeted agent,[59] and dianhydrogalactitol (VAL083), a bifunctional alkylating agent,[60] but results are still very preliminary. Berubicin (RTA744) is a novel, synthetic, second-generation anthracycline that uses natural processes to induce DNA damage in targeted cancer cells by interfering with the action of topoisomerase II, a critical enzyme enabling cell proliferation. It is designed to circumvent P glycoprotein/MRP1-mediated efflux and is not only a more potent topoisomerase II inhibitor than doxorubicin but is also able to cross the BBB.[61] In a Phase I trial in recurrent GB, 12 of the 35 patients (48%) attained longer PFS.[62] In 2020, the US FDA granted Orphan Drug Designation to berubicin for the treatment of recurrent GB and granted it Fast Track Designation in 2021. An ongoing phase II trial (ClinicalTrials.gov NCT04762069) is comparing berubicin versus lomustine in recurrent GB.

Targeted Therapy

EGFR alterations are present in many GBs (50% with *EGFR* overexpression, 40% with *EGFR* amplification, 6–13% with fusions).[63] The most common mutation is *EGFR* vIII, which promotes cell proliferation, angiogenesis, and tumor invasion.[64] *EGFR* and *EGFR* vIII transduce signals via the RAS/RAF/MEK/ERK, *PI3K*/*AKT*, JAK/STAT, and PKC pathways. *EGFR* has been targeted with multiple therapies with different mechanisms of action, including tyrosine kinase inhibitors, antibodies, vaccines, CAR T-cells, bispecific T-cell engaging antibodies targeting *EGFR* vIII, and RNA-based therapies. To date, however, none of these targeted therapies has improved patient outcome.[65,66] Nevertheless, the importance of *EGFR* alterations is clear and new agents are being tested, for example in the INSIGhT trial and in a phase I trial of RO7428731 (ClinicalTrials.gov NCT05187624).

The *PI3K*/*AKT*/*mTOR* pathway is also frequently altered. Different attempts have been made to target *PI3K, AKT* and/or *mTOR* with different drugs, but none has succeeded in improving outcome, meeting study endpoints, or translating promising results from cell line or xenograft models to convincing results in randomized studies, probably due to molecular compensatory mechanisms, crosstalk between signal pathways, or tumor heterogeneity.[67–70] Nevertheless, due to the importance of this pathway in GB, research on new agents continues in early-phase trials,[71,72] and other agents, such as CC-115, are being tested in the INSIGhT trial and in several phase I trials (ClinicalTrials.gov NCT02133183, NCT02142803).

The *pRB* cell cycle control pathway, which controls cell cycle progression, is often disrupted due to *CDK4/6* amplification or *CDKN2A/B* loss or mutation.[73] The CDK4 and CDK6 complex with cyclin D drives the phosphorylation of the retinoblastoma protein, which allows the cell to commit to division.[74,75] Palbociclib, a CDK4/6 inhibitor approved for the treatment of breast cancer[76] failed to provide a benefit in a phase II trial.[75] Other CDK4/6 inhibitors are being tested, such as zotiraciclib (ClinicalTrials.gov NCT03224104, NCT02942264), and abemaciclib is being examined in the INSIGhT trial[77] and in a phase I trial (ClinicalTrials.gov NCT04074785).

TP53 is involved in cell cycle progression and induction of apoptosis. Since the key function of its gene product, P53, is to arrest cells in G0/1 or to trigger apoptosis in response to genotoxic stress, various approaches have tried to restore P53 function but without success. The MDM2 protein binds to P53, preventing its action and transporting it from the nucleus to the cytosol. MDM2 also covalently attaches ubiquitin to P53, thus marking P53 for degradation by the proteasome. Several ongoing trials are focusing on neutralizing MDM2 and MDM4 in GB patients who lack P53 function due to *MDM2* or *MDM4* gene amplification.[78]

Mutations of mismatch repair (MMR) genes, especially *MSH6*, are common in relapsed GB and may impact response to temozolomide. Loss of expression of MSH6 and other MMR proteins was found in about 25% of GB patients at relapse but rarely at diagnosis, and there was no correlation with microsatellite instability (MSI). Totally deficient MMR (dMMR) tumors had a hypermutated genome,[79] suggesting that loss of MMR proteins may be a surrogate of hypermutation in high-grade gliomas. Patients with dMMR and high MSI are immunogenic as they harbor thousands of somatic mutations that trigger the upregulation of immune checkpoint proteins. Pembrolizumab is active in non-colorectal dMMR/MSI tumors but not in relapsed dMMR GB patients.[80] It is currently being tested in combination with radiotherapy and with other agents (ClinicalTrials.gov NCT03661723).

Proteasomes regulate cell survival, cell cycle progression, gene transcription, antigen presentation, and DNA repair.[81] Proteasome inhibitors, such as bortezomib, carfilzomib, ixazomib and marizomib, interfere with this activity and may disrupt various cellular processes, stopping proliferation and leading to cell death. Bortezomib was tested in GB without success, probably because of low penetration into the brain.[82] However, marizomib, an irreversible inhibitor of the beta-lactone class that binds to the catalytic moieties of the proteasome, can cross the BBB and has shown promising activity in preclinical and xenograft models. The encouraging results of a phase I trial of marizomib in combination with bevacizumab (ClinicalTrials.gov NCT02330562) led to a phase II study (ClinicalTrials.gov NCT02903069) and then to the randomized Phase III Mirage trial in newly diagnosed GB, where it was added to the standard radiotherapy/temozolomide regimen. Unfortunately the results of this trial have been clearly disappointing regarding outcome, and marizomib-related neurological and psychiatric toxicities were quite significant.[83]

IDH1 and *IDH2* mutations are present in about 10% of GBs diagnosed according to the WHO 2016 classification,[84] but these tumors are now classified as grade 4 astrocytoma[85] and have a better prognosis even in the recurrent setting.[86] Nevertheless, due to the importance of this alteration in gliomas, research on targeting IDH is continuing while the new classification is adopted for pathological diagnosis.[63,87] Several early-phase studies targeting IDH are ongoing; most include low-grade gliomas but not all of them limit inclusion to this grade. Ongoing or recently finished phase I studies have examined first-generation IDH1 inhibitors like ivosidenib (AG-120), BAY-1436032, DS-1001b, IDH305 and olutasidenib (FT2102), the second-generation IDH1 inhibitor LY3410738, the IDH2 inhibitor enasidenib (AG-221), and the dual IDH1/2 inhibitor vorasidenib (AG-881). In addition, several peptide vaccines, such as the IDH1(R132H) peptide vaccine PEPIDH1M, and an autologous dendritic cell vaccine are testing the safety and efficacy of targeting IDH1/2.[88–90]

PARP proteins are involved in the base excision repair (BER) pathway. It has been postulated that PARP inhibitors could enhance the efficacy of the standard treatment in GB since the combination of temozolomide and PARP inhibitors could increase cytotoxic effects.[91] BER repairs most radiation-induced single-strand DNA breaks, suggesting that PARP inhibitors could also act as radiosensitizers.[92,93] Moreover, since GB stem cells increase tumor aggressiveness, confer chemo- and radioresistance, and have a high DNA repair capacity, PARP inhibition could also be a good strategy to ameliorate these effects. Several studies have demonstrated that PARP inhibitors have the ability to reach GB margins[94,95] and some early-phase clinical trials have been carried out, but with variable results (ClinicalTrials.gov NCT04614909, NCT03914742, NCT03749187, NCT05076513).[96,97]

HIF-1 is a transcription factor regulated by the presence or absence of oxygen. Under hypoxic conditions, HIF-1α is stabilized and dimerizes with HIF-1β, after which it translocates to the nucleus to act as a transcription factor controlling the expression of hundreds of genes.[98,99] HIF-1 promotes the expression of proangiogenic factors, such as VEGF, angiopoietin, and erythropoietin,[100] promotes tumor cell migration, and enhances tumor cell autophagy.[101] Several approaches to inhibit the hypoxia pathway have been explored. EZN-2698, a HIF-1 α inhibitor failed to demonstrate a clinical benefit in solid tumors.[102] Panobinostat and vorinostat effectively induced HIF-1 degradation,[103] but they inhibit all class I histone deacetylases, making them very non-specific. Other approaches have looked at blocking the interaction of HIF-1α with its co-activators, thus antagonizing hypoxia-inducible transcription.[98] However, despite these diverse strategies, only a few molecules have shown a good safety profile in early-phase studies, and efficacy is limited in refractory solid tumors (ClinicalTrials.gov NCT02974738).

Other targets are being explored in preclinical models and phase I studies. Some are not specific to GB but are commonly altered in cancer. Some of the alterations that are currently being studied are: Bruton tyrosine kinase, arginine, the XPO protein, C-Met, BET, AXL-UFO, farnesyltransferase, STAT, cerebron, SHH, DRD2 antagonist/ClpP agonist, SMO/SHH, tryptophan and its associated enzymes, and IDO1/2. However, these studies are in the initial stages and no results are yet available. At the same time, other potential targets in GB, such as TERT promoter mutations, which are involved in cell proliferation and longevity, are yet to be explored.[73] At present, unfortunately, no agent is envisioned to succeed in a phase III study and become a standard of care.

Radioligand and Boron Neutron Capture Therapy (BCNT)

Radioligand therapy is an innovative approach that combines a radioligand, which locates cancer cells, with a radioisotope, which is a therapeutic radioactive particle. The radioligand binds to cancer cells anywhere in the body and emits targeted radiation, directly attacking the tumor. Radioligand therapy is well established as a treatment modality for advanced gastroenteropancreatic neuroendocrine tumors and is being studied for some types of prostate cancer and other solid tumors, including breast, lung and brain. [^{177}Lu]Lu-NeoB binds to the gastrin-releasing peptide receptor (GRPR) through the NeoB peptide, which contains a DOTA metal chelator that allows radiolabeling with different radionuclides.[104] GRPR is present in various glioma cell lines and a correlation has been observed in glioma patients between SUV and GRPR expression.[105] A phase I study is being completed (ClinicalTrials.gov NCT05109728) and a randomized trial comparing [^{177}Lu]Lu-NeoB versus carmustine in recurrent GB is planned.

Boron neutron capture therapy (BNCT) combines biological targeting and low-energy thermal neutrons. Kawabata et al demonstrated acceptable safety and prolonged survival for recurrent GB in a phase II trial involving 27 patients compared with results with bevacizumab.[106] Although preliminary clinical results of BNCT are promising, further research is needed in order to find more selective boron compounds.[107]

Immunotherapy

Unfortunately, initial results with immunotherapy have been disappointing. Several factors have been postulated as the cause of this resistance to immunotherapy: low tumor burden; immunosuppressive microenvironment (macrophages, myeloid-derived suppressor cells, microglia, T cell exhaustion); tumor heterogeneity (antigen escape); the BBB; and systemic immunosuppression (corticosteroids, lymphopenia). A better understanding of resistance mechanisms to immunotherapy would provide insight into effective strategies.[108–111] Four different types have been studied in GB: immune checkpoint inhibitors (ICIs), vaccines, chimeric antigen receptor (CAR) T-cell therapy and oncolytic viruses.

Immune Checkpoint Inhibitors

Three phase III randomized trials have explored the benefit of ICIs in GB – one in the recurrent setting[112] and two in newly diagnosed GBs.[113,114] In a trial comparing nivolumab with bevacizumab in the recurrent setting, no differences in survival were found although more durable responses were observed in the nivolumab arm (10 vs 5 months). However, fewer than 10% of patients in the nivolumab arm attained a radiographic response compared to 23% in the bevacizumab arm.[112] Neither of the two trials in newly diagnosed GB met their primary endpoint of differences in OS.[113,114] Several phase II trials have also examined ICIs in GB. A study comparing pembrolizumab alone versus pembrolizumab plus bevacizumab in recurrent GB found that pembrolizumab was ineffective both as monotherapy and in combination with bevacizumab.[115] Neoadjuvant trials of ICIs have reported intriguing results, showing clonal expansion of T cells and overexpression of interferon-gamma and T cell related genes, suggesting a potential benefit in this setting.[116]

Vaccine Therapy

Several vaccine therapies have been explored in GB, including peptide/multipeptide vaccines and dendritic cells. The aim of vaccine therapy is to induce an immune response against tumor antigens in order to eliminate GB cells. There are two types of antigens: tumor-associated antigens (TAA), which are expressed in both normal and tumor cells, and tumor-specific antigens, which are expressed only in tumor cells.[117,118] Some TAAs have been explored in clinical trials with the aim of activating GB immunogenicity, which depends on the affinity of the antigen for major histocompatibility complex and the sequence length. A vaccine against EGFR vIII, rindopepimut®, showed promising results in early clinical trials but failed to demonstrate any benefit in a phase III trial.[65] A vaccine against IDH1(R132H) that was tested in a phase I trial in newly diagnosed GB induced T cell and B cell immune responses, and vaccine-induced immune responses were observed in 93.3% of patients.[119] A randomized trial is warranted to confirm these results. Multipeptide vaccines may be more active. A phase I study of IMA950, a GB-specific vaccine containing 11 tumor-associated peptides, met its primary immunogenicity endpoint.[120] Several other trials of multipeptide vaccines are ongoing but in initial stages.

Dendritic cells can be used to activate innate and acquired immunity. Monocytes need to be isolated from a patient's peripheral blood, after which GM-CSF and IL-4 are used to induce immature dendritic cells. Then tumor antigens or patient-derived tumor lysates are loaded into the cells.[121] A randomized phase III trial in newly diagnosed GB patients found that (DCVax®-L) conferred longer OS in all patients, especially in those with *MGMT* methylation. However, crossover had led to 90% of the patients receiving the vaccine, making it difficult to draw definite conclusions.[122] In a recent report the 64 patients with recurrent WBC who crossed over to DCVAX treatment had an mOS of 13.2 (95% CI, 9.7–16.8) months from relapse vs 7.8 (95% CI, 7.2–8.2) months among control patients (HR, 0.58; 98% CI, 0.00–0.76; $P < 0.001$).[123] Methodological problems in the study design obscure these results.[124] ICT-107 is an autologous dendritic cell vaccine pulsed with six synthetic peptide epitopes targeting GB tumor/stem cell-associated antigens (MAGE-1, HER-2, AIM-2, TRP-2, gp100, and IL13Ra2). A randomized placebo-controlled phase II trial of ICT-107 in newly diagnosed GB patients showed a two-month benefit in PFS but no impact on OS.[125] Two recent meta-analyses of dendritic cell vaccines in GB have reported conflicting conclusions as to the benefit of these vaccines.[126,127] In summary, vaccine therapy may prove to be a beneficial strategy in GB but results to date are not promising. Moreover, the high cost of vaccines and difficulties associated with their manufacture could hinder their use in clinical practice.

Chimeric Antigen Receptor (CAR) T-Cell Therapy

CAR T-cell therapy relies on genetically modified T cells that express CARs engineered to recognize cancer-associated cell surface antigens. CAR T-cell therapy has revolutionized the treatment of lymphoma and acute leukemia and is now being explored in other hematological and solid tumors. Several ongoing early-phase trials evaluating the safety and feasibility of CAR T-cell therapy in GB have found an acceptable safety profile when administered intravenously or intracranially but efficacy data are limited.[128] Different antigens have been used in CAR T-cell therapy, including IL13Ralfa2, EGFRvIII, HER2 and B7-H3. Clinical benefit has been generally short-term, probably because of antigen loss relapses. Glioblastoma tumor heterogeneity is a challenge in this type of therapy and new strategies are under investigation, such as multiple antigen targeted CAR T cells with co-stimulatory molecules and immunostimulatory

cytokines.[129,130] Several ongoing clinical trials are exploring the combination of CAR T-cell therapy with ICI or with treatments targeting tumor-associated macrophages like anti-CSF-R1. New CAR-engineered natural killer cells are also being studied in GB.[128]

Oncolytic Viruses

Oncolytic viruses are genetically modified to be able to infect and replicate into the tumor mass, thus exerting a selective tumor lysis and inducing an antitumor immune response. The promotion of a "hot" tumor microenvironment could be crucial in increasing tumor responses to oncolytic viruses, either as monotherapy or in combination with other immunotherapies.[131,132] Oncolytic viruses are generally administered locally during surgery to overcome the BBB although preclinical studies have demonstrated that they can be loaded on stem cell carriers and delivered to malignant glioma tumors when injected systemically.[132] Several candidate viruses have been engineered to treat GB, including retrovirus, adenovirus, herpes simplex, reovirus, parvovirus, vaccinia virus, Newcastle disease and poliovirus.

Oncolytic viruses have shown promise in phase I/II trials. ONYX- 015 induced immune responses, and both the oncolytic adenovirus DNX-2401 (tasadenoturev)[133] and the non-pathogenic polio-rhinovirus chimera (PVSPIRO) induced immune and clinical responses.[134] These viruses had a good safety profile and promising efficacy in recurrent GB: 20% of patients survived more than 3 years.[134,135] In contrast, after promising results with Toca 511 in an early phase I trial, with 20% of durable (>24 weeks) complete responses, no survival benefit was observed in a phase III trial of 403 patients.[135]

Recently, interesting data have been reported from phase I/II studies of two oncolytic herpes simplex virus-1 (HSV-1): a phase I trial of the HSV-1 G207 for pediatric high-grade gliomas[136] and a phase II trial of the HSV-1 G47Δ for residual or recurrent GB in Japanese patients.[137] The Japan Ministry of Health granted conditional approval to teserpaturev® (G47Δ; Delytact), a triple-mutated, third-generation oncolytic HSV-1, for intratumoral administration in malignant glioma. G47Δ is the first oncolytic virus to receive approval for this use. However, the trial included only 19 patients, the increase in OS was only compared to historical controls, and six of the 19 patients were IDH1-mutated. Therefore, according to internationally accepted rules, a randomized phase III trial should be launched to validate these results.

Two phase II clinical trials have been carried out in the replication-deficient adenovirus mutant thymidine kinase (ADV-TK). ADV-TK administered by intra-arterial cerebral infusion in combination with ganciclovir conferred longer PFS and OS in a series of 53 recurrent GB patients.[138] In a subsequent multicenter trial in the first-line setting, ADV-TK was combined with valacyclovir and administered at surgery, but only a non-significant benefit was observed, especially for patients with gross total resection.[139] Several studies of different oncolytic viruses and different treatment schemes are now including patients (ClinicalTrials.gov NCT03714334, NCT02457845, NCT03896568).

Discussion and Future Prospects

Challenges in the Search for New Treatments

Identifying effective treatments in GB has long been a difficult task due to various impediments. In addition to the low incidence of the disease itself and the characteristics and symptoms of the patients that preclude their participation in clinical trials, there are other obstacles to clinical research. In fact, the prognosis of GB is so poor that – contrary to common practice in other cancers – new treatments are often tested first in newly diagnosed patients rather than in recurrent disease.

One of the main handicaps is the difficulty in delivering reasonable therapeutic doses to the tumor because of the BBB and the brain-to-tumor barrier (BTB), which are protective biological mechanisms of the brain that block potentially toxic agents from reaching the brain.[140,141] The BBB is a tight network of endothelial cells, astrocytes and pericytes that regulates the delivery of nutrients, metabolites and xenobiotics from the blood to the CNS. It restricts the passage of 100% of macromolecules and almost 98% of smaller molecules into the CNS. The modifications that GB exerts on this barrier constitute the BTB, which is highly variable in structure and leads to a disorganized formation of new vessels and to a decrease in the tight junctions between the cells that form the barrier. As a result, the permeability of the BBB increases heterogeneously, as can be seen in MRI gadolinium sequences, which hinders the uniform distribution of drugs.[140] In addition to the BBB and BTB, the local microenvironment can prevent the diffusion of the treatment

within the brain. The microenvironment is formed by an extracellular matrix consisting of a mixture of collagen, elastin, proteoglycans and hyaluronic acid, together with low oxygen and pH levels that promote invasiveness and chemoresistance of the GB cells, thus diminishing the effect of treatment.[142,143] Importantly, drug distribution into cerebrospinal fluid (CSF) is not a measure of BBB transport since drugs injected into CSF are not distributed to the inner parenchyma of the brain but to the blood, and drug concentrations in the brain are much lower than in CSF or blood.[144]

Given these hindrances, there will always be doubts as to whether a drug will reach the tumor in sufficient concentrations to be effective. Research on different delivery methods, including local therapies and methods to modify the permeability of the BBB, has been ongoing for years.[145,146] Window of opportunity studies could play an important role in alleviating this situation because they measure drug levels in the tumor by administering the drug after biopsy and prior to surgical resection. However, the aggressiveness of two surgical procedures in the same patient together with the potential complications inherent in any cerebral surgical maneuver will hamper the widespread use of this type of trial.[147]

Another source of difficulty is the potential metabolic interaction between the drugs under study and the drugs that patients require to control their symptoms, such as anticonvulsants, antidepressants and corticosteroids, which can act either as inducers of metabolism, thus decreasing the effective doses of the antitumor drugs, or as inhibitors of metabolism, thus increasing the drug-related toxicity.[148]

In addition to problems associated with drug delivery and interaction, there is a need first to identify the molecular target whose inhibition will stop tumor growth among all the potential molecules that have been identified in GB.[149,150] and then to determine the optimal treatment to inhibit or block the target.

A further challenge lies in measuring treatment response and determining clinical benefit, which can affect the choice of the primary endpoint of a clinical trial, which in turn can determine the acceptance of the trial results by the oncology community and medicine agencies. A clear example of the importance of the primary trial endpoint and the consequent difficulties in bringing a drug to the therapeutic arena is the case of bevacizumab. Despite having achieved an increase in PFS in all the studies, an objective that has been accepted in many tumors, it was not approved by the EMA because the main objective of the trials was to increase OS, not PFS. As a result, in Europe, bevacizumab is used only for compassionate use.[151]

Measuring response to treatment has always been difficult in GB because there are several confounding factors. On the one hand, at recurrence, all patients have already received local irradiation. The irradiated lesions are usually considered not measurable in the RECIST guidelines used for other tumors[152] unless a clear progression is demonstrated. Brain irradiation produces changes on the MRI that make it difficult to differentiate between tumor progression, pseudoprogression and radionecrosis.[153] In addition, neurological damage caused by the tumor does not usually subside once a response is obtained, and the size of the tumor is not related to the patient's clinical condition, which depends more on the location of the tumor in eloquent or non-eloquent areas.[154] To overcome these drawbacks, the international neuro-oncology community has developed the standardized RANO response criteria, which are based not only on MRI evaluation, including standardization of sequences, but also on the patient's neurological status and the doses of dexamethasone needed, whose irreversible increase is usually related to tumor progression.[155–157] The neuro-oncology community is continuously making an effort to determine the best design for clinical trials regarding both the selection of the primary endpoint (therapeutic response, PFS at 6 or 12 months, OS) and the magnitude of benefit that is acceptable to change standard of care.[158–160]

In fact, even though GB treatment guidelines recommend inclusion in clinical trials,[3] only a minority of patients are fit enough to be included.[6] Efforts are now directed towards identifying the barriers to inclusion and increasing participation.[158,160]

Another difficulty that we will encounter in the near future stems from the reclassification of GB (as defined by the 2016 WHO criteria)[84] into different entities by the recent 2021 WHO classification.[85] Glioblastomas with IDH1/2 mutations are now classified as grade 4 astrocytomas, with a considerable better prognosis; those located in midline structures and harboring H3p.K28M (K27M) mutations are now diffuse midline gliomas H3K27; and hemispheric GBs with H3 G34 mutations are now classified as diffuse hemispheric gliomas H3G34. Additionally, GBs with wild-type H3 and IDH1/2 are now classified as diffuse pediatric-type high-grade glioma H3 and IDH wild-type. These are mainly found in young adults and have different outcomes but may exhibit necrosis and vascular proliferation, which suggests

that they could have been included in trials of GB in the past. In addition, some IDH wild-type histologically low-grade gliomas with *TERT* promoter mutations or *EGFR* gene amplification or a +7/−10 genotype are now reclassified as GBs even in the absence of vascular proliferation or necrosis. It is still not clear if these newly reclassified GBs will be included in trials of GB IDH wild-type because their prognosis is not exactly the same.[63,161] The predicted treatment response and outcome of these new tumor types have been drawn from previous trials in which tumors were classified primarily by histology. However, it may well be that these subtypes will not be included in future trials, which will further reduce the number of patients who are candidates for inclusion and will make it impossible to determine if the new therapies are effective in these entities. As a result, it will be even more difficult to conduct phase III trials requiring large numbers of patients.

Finally, immediate and delayed drug-related toxicity, especially that affecting neurocognitive function, must be taken into account when deciding on therapy. If a drug manages to break through the BBB and BTB but causes neurological damage to healthy cells, survival benefit will increase but quality of life will not be maintained and there will be no clinical benefit. Therefore, it is essential to consider quality of life, patient reported outcome, and toxicity before implementing a new treatment in clinical practice.[160,162]

New trial designs are aimed at a rapid identification of agents that are suitable for study in phase III trials in order to accelerate research in new clinical therapies for GB. For example, the phase II randomized INdividualized Screening Trial of Innovative Glioblastoma Therapy (INSIGhT, ClincalTrials.gov NCT02977780) is comparing a control arm of standard first-line treatment with different experimental arms, while the international, seamless phase II/III AGILE trial is an adaptive response Bayesian randomization platform designed to evaluate multiple therapies in newly diagnosed and recurrent GB.

In conclusion, although GB prognosis remains gloomy and no new treatments have proven effective, there are many ongoing lines of research. As our knowledge of genomic data grows, we will have a better understanding of resistance mechanisms, which should lead to advances in therapy. However, there is clearly still a great deal of work to be done in GB.

Disclosure

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