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Updates for newly diagnosed and recurrent glioblastoma: a review of recent clinical trials

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Purpose of review
Glioblastoma (GBM) is the most common and devastating primary malignant brain tumor. We summarize recent advances in radiotherapy, immunotherapy, and targeted therapy approaches for the treatment of newly diagnosed and recurrent glioblastoma. We also introduce ongoing clinical trials.

Recent findings
Recent clinical trials have explored multiple novel strategies to treat GBM including the use of oncoviruses, chimeric antigen receptor (CAR) T cell therapy, vaccines, radiotherapy, and novel drug delivery techniques to improves drug penetrance across the blood brain barrier. Approaches to improve drug delivery to brain tumors have the potential to expand treatment options of existing therapies that otherwise have poor brain tumor penetrance. Immunotherapy has been of keen interest in both newly diagnosed and recurrent glioblastoma. Vaccines SurVaxM and DCVax-L have shown initial promise in phase II and III trials, respectively. CAR T cell therapy trials are in their early phases but hold promise in both newly diagnosed and recurrent glioblastoma.

Summary
Although progress to improve outcomes for GBM patients has been modest, multiple novel strategies utilizing combination therapies, focused ultrasound to improve drug delivery, and novel immunotherapies are underway.

Keywords
chimeric antigen receptor T cell therapy, focused ultrasound, Glioblastoma multiforme, oncoviruses, radiotherapy

INTRODUCTION

The standard of care for glioblastoma (GBM) has remained relatively unchanged for the last 20 years. Standard of care for newly diagnosed GBM (nGBM) includes maximal safe resection, followed by radiation therapy (RT) with concurrent and adjuvant temozolomide chemotherapy with or without tumor treating fields (TTF) [1]. Median overall survival (mOS) ranges from 16 to 21 months; however, O6-methylguanine-DNA-methyltransferase (MGMT) methylation status also notably impacts survival. mOS in methylated GBM is 18.4 months compared to 10.8 months in unmethylated GBM [2,3]. TTF was the most recent therapy to be approved for nGBM management, which improved mOS to 20.5 months [3]. Recent clinical trials have sought to address the relative worse prognosis and lack of efficacy of temozolomide for unmethylated MGMT nGBM.

Currently, there is no standard of care for recurrent GBM (rGBM),which has a particularly grim prognosis with estimated mOS from time of recurrence of 3–11 months [4]. Enrollment in clinical trials is prioritized but often limited by number of prior therapies and other stringent criteria [5]. Temozolomide rechallenge, lomustine, bevacizumab, repeat resection, and reirradiation are all utilized in eligible patients. In this review, we will discuss recent clinical trials published over the last 18 months for nGBM and rGBM treatment.

NEWLY DIAGNOSED GLIOBLASTOMA

Vaccines

Two recently published trials include SurVaxM in a phase II trial and DCVax-L in a phase III trial.

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KEY POINTS

- Focused ultrasound can expand therapeutic exploration into existing cancer therapies that were previously limited by blood brain barrier penetration.
- Though immunotherapy in general has been disappointing in the treatment of newly diagnosed and recurrent glioblastoma (GBM), chimeric antigen receptor (CAR) T cell therapy continues to be explored in early phase clinical trials.
- The dendritic cell vaccine, DCVax-L, was the only positive phase III clinical trial in GBM therapy in the last 18 months; however, results should be interpreted cautiously due to study protocol changes and comparison to historical controls. A follow up phase III clinical trial comparing DCVax-L to standard of care with placebo vaccines is ongoing.

SurvaxM is a synthetic conjugated vaccine targeting survivin, a fetal antigen that is highly expressed in malignant gliomas [6,7]. SurVaxM may enhance or trigger an immune response to tumoral surviving [8]. The phase I trial for SurVaxM included nine patients with recurrent high-grade gliomas and found four doses administered once every 2 weeks was overall well tolerated without reported serious adverse events [6]. mOS in this cohort was 20 months with seven of nine patients surviving >1 year after study entry [6]. Given the tolerability and promising phase I results, a phase II study followed with a larger cohort of nGBM patients. These patients received their first dose of SurVaxM within 4 weeks of completing chemoradiation and three subsequent doses every two weeks. This was followed by a maintenance phase, where patients received additional doses every 12 weeks until disease progression or treatment intolerance. Median progression free survival (mPFS) and mOS from time of diagnosis was 14.4 months and 28.4 months, respectively. Additionally, 6-month progression free survival (PFS) was 95.2%, significantly longer than a comparison control cohort of 54% ($P < 0.0001$). Posthoc subgroup analysis of MGMT methylation status revealed MGMT methylated patients had a mOS of 41.4 months compared to 16.5 months in unmethylated patients [8]. Given the positive mPFS and mOS data, additional SurVaxM studies are underway including the randomized, blinded phase II SURVIVE trial (NCT05163080) comparing SurVaxM with temozolomide against temozolomide alone in nGBM after completion of chemoradiation.

There is additional cause for optimism with the results of the phase III trial of DCVax-L, a dendritic cell vaccine. Dendritic cell vaccines expose dendritic cells to tumor antigen, which triggers adaptive immune system T cells to attack tumor cells and prevent growth recurrence [9]. This phase III trial enrolled both nGBM and rGBM patients and compared DCVax-L plus standard of care compared to a historical control group receiving standard of care alone. mOS for the DCVax-L in the nGBM group was 19.3 months from trial randomization, which was significantly longer than in the control group with mOS of 16.5 months ($P = 0.02$). The relative benefit increased over time. For example, survival at 60 months from randomization was 13.0% in the DCVax-L group vs. 5.7% in the standard of care control group. The rGBM arm reflected similar results with mOS of 13.2 months from recurrence in the DCVax-L group vs. 7.8 months in the standard of care group ($P < 0.001$), with persistent survival benefit over time [10▪▪]. Although these results are promising, several challenges limit the interpretation of the results including multiple amendments to the protocol to allow cross over from placebo to DCVax-L, change in the primary endpoint, and a late change to compare outcomes with a historical control group. A study is ongoing to compare DCVax-L with standard of care with internal controls receiving standard of care with a placebo vaccine in nGBM (NCT00045968).

Chimeric antigen receptor-T therapy

Chimeric antigen receptor T (CAR T) cells have changed the landscape of hematologic malignancies, and subsequently prompted exploration into the applicability of CAR T cells in other cancers, including GBM. CAR T cells are generated by engineering a patient's own T cells to attack a specific tumor antigen [11]. Research is ongoing to advance these approaches including a phase I trial of EGFRvIII CAR T cells with concurrent pembrolizumab after resection and a hypofractionated radiotherapy (HFRT) approach of 40 Gy in 15 fractions (NCT03726515). The combination was well tolerated without dose limiting toxicities noted in the seven patients enrolled; however, the CAR T cell number increased after pembrolizumab infusions but were not persistent, the immune compositions of the tumors did not change, and CAR T cells were found in only one patient's tumor at time of repeat resection. This raises questions of pembrolizumab possibly hindering CAR T cell expansion, the role of lymphodepleting chemotherapy in CAR T therapy, and the role of residual tumor post-resection to allow for CAR T cell proliferation [12].

Radiotherapy

Recent RT trials in nGBM have focused on hypofractionated radiotherapy (HFRT) and stereotactic

radiosurgery (SRS) especially in the elderly population [13▪,14]. The goal of HFRT is to reduce treatment duration using higher doses per fraction, and subsequently improve quality of life [15]. Long term follow up was recently published from a randomized trial of standard of care vs. RT of 60 Gy over 20 fractions which continued to show no statistically significant improvement in mOS (26.5 vs. 22.4 months, $P = 0.122$) or PFS (14.3 vs. 13.2 months, $P = 0.417$) 6 years after intervention [16]. Additionally an early phase trial of SRS in nGBM evaluated dose escalation safety and smaller 5 mm margins compared to conventional 20 mm margins. Patients underwent maximal safe resection, RT, and adjuvant temozolomide. 63% of patients experienced tumor recurrence within the SRS field, 11% recurred between 5 and 20 mm, and 26% recurred beyond 20 mm. When comparing delivered RT to standard 20 mm margins, only 1 patient had recurrence between 5 and 20 mm that may have been treated with conventional margins [13▪]. Two patients experienced dose limiting toxicities; one included intracranial postsurgical hemorrhage 2 weeks after SRS at 40 Gy [17]. Radiation necrosis occurred in 26% of patients and significantly correlated with in-field tumor control ($P = 0.003$). Though not statistically significant, mOS for patients with tumor necrosis was 27.2 months compared to 11.7 months in those without necrosis ($P = 0.077$) [13▪]. These studies identify additional questions regarding optimal radiation margins and dose escalation protocols. Studies are ongoing to evaluate the use of SRS with other GBM treatments such as TTF (NCT04474353) and immunotherapies (NCT04977375, NCT04225039, NCT04729959).

Targeted therapies

Although previously presented, results were published of the randomized phase III clinical trial of depatuxizumab mafodotin (depatux-m), an EGFR monoclonal antibody that delivers a cytotoxic payload once endocytosed (NCT02573324). In this phase III trial evaluating depatux-m with temozolomide vs. temozolomide alone in nGBM with EGFR amplification, PFS was prolonged in the depatux-m group (8.0 months) when compared to temozolomide alone (8.0 vs. 6.3 months, respectively, $P = 0.029$); however, mOS was no different between groups (HR 0.95, $P = 0.76$) [18]. Additionally, 12% of patients in the intervention arm discontinued depatux-m due to corneal epitheliopathy, a known adverse effect [18].

Veliparib is a poly ADP-ribose polymerase inhibitor thought to enhance the effects of temozolomide through inhibition of DNA repair [18,19]. A phase I trial assessing veliparib in combination with chemoradiation was terminated early after 3 of 12 patients in the initial cohort developed severe thrombocytopenia. Despite dose reduction, an additional two patients developed dose limiting thrombocytopenia, and one developed neutropenia. Due to these toxicities, the investigators ended the trial [19]. Final results from the phase II/III veliparib trial in newly diagnosed MGMT promotor methylated GBM (NCT02152982) were also negative; the trial failed to show any significant benefit to mOS and mPFS [20].

RECURRENT GLIOBLASTOMA

Improving drug delivery

One major hurdle to effectively treating brain tumors is the limited delivery of drugs across the blood–brain barrier (BBB). One promising approach to enhance drug delivery uses low intensity focused ultrasound (LIFU) [21]. Several recent clinical trials have evaluated the use of LIFU-mediated BBB disruption.

In an early phase I clinical trial, LIFU devices were implanted to replace the skull following recurrent GBM resection. Three, six, or nine emitters in the device were activated, which corresponded to greater total volume sonicated. Sonication was used to enhance delivery of i.v. carboplatin chemotherapy administered before or after sonication. Device placement and activation were safe and well tolerated [22,23▪]. BBB disruption caused by LIFU was confirmed by a significant and exponential increase in MRI gadolinium contrast enhancement when contrast was administered 10 min to 77 min post sonication [23▪,24]. Calculated BBB half-closure time was 1.3 h [23▪]. A significantly slower tumor growth rate was seen in the cohort that received carboplatin immediately prior to sonication when compared to the group that received carboplatin after sonication (0.54 ml/month vs. 2.31 ml/month, respectively, $P = 0.04$) [23▪]. Sonication and BBB disruption research is ongoing, and clinical trials with results pending include therapeutic focused ultrasound in newly diagnosed and rGBM with or without chemotherapy. Another study is evaluating focused ultrasound as a diagnostic tool to enhance liquid biopsy sensitivity in serum in suspected glioma patients (NCT05383872).

Immunotherapy

Despite their success in other tumor types, recent immunotherapy studies in GBM over the last decade have been disappointing. Nivolumab vs. bevacizumab in rGBM, nivolumab with RT in

unmethylated nGBM, nivolumab with temozolomide and RT in methylated nGBM, and pembrolizumab alone or in combination with bevacizumab in rGBM were all negative studies failing to improve mOS [25–28].

Methods to improve neoantigen exposure and response to checkpoint inhibitor efficacy are being pursued. A phase I clinical trial evaluated avelumab alone and after laser interstitial thermal therapy (LITT) to increase neoantigen release. The LITT followed by avelumab group had an increase adverse event of cerebral edema reflected by receiving more and higher doses of dexamethasone. In secondary analyses of patients with survival >12 months, investigators found that five of six participants received bevacizumab in combination with avelumab [29]. Bevacizumab may have had an impact on outcome; however, conclusions should be drawn cautiously in the setting of low sample size not designed to evaluate this interaction.

Trotabresib inhibits bromodomain and extraterminal (BET) proteins involved in cancer cell proliferation which is overexpressed in glioma [30,31]. A recent phase I clinical trial assessed the safety and brain penetrance of trotabresib. Nineteen of 20 patients enrolled had rGBM. All patients were given trotabresib prior to planned surgical resection and tissue was analyzed for brain tumor drug concentration. Sixteen patients continued study treatment post operatively receiving trotabresib monthly. No serious treatment related adverse events were reported; two patients died of surgical complications reported to be independent of the study treatment. Mean tissue:plasma ratio was 0.84, suggesting adequate BBB penetrance. The 6-month PFS rate was 12% and mPFS was 1.9 months; two patients remained on study drug with radiographically stable disease [32]. Given these findings, additional studies are underway to assess trotabresib in nGBM.

CAR-T cell therapy is highly efficacious in, and FDA approved for numerous hematologic malignancies; however, their efficacy in solid tumors including GBM has been more limited [33]. GD2 is expressed in both normal neuronal and malignant glioma tissue. Prior preclinical and early phase studies of GD2 CAR T showed efficacy and specificity for GD2 positive tumors [34,35]. In this phase I study, patients with GD2 positive tumor by immunohistochemistry were enrolled. Patients who underwent surgical resection for rGBM received both intracavitary and intravenous GD2 CAR T therapy, while those who did not undergo surgical resection received intravenous GD2 CAR T therapy alone. 3 patients received intravenous and intracavitary infusions, while 5 received intravenous infusions alone. GD2 CAR T cells were detected in peripheral blood in all patients at 4 weeks post infusion. mOS after the study intervention was 10 months. Intravenous and intracavitary GD2 CAR T infusions were safe and well tolerated. Though no conclusions were drawn between intravenous vs. intracavitary infusions owing to the small sample sizes, the three patients who received both intravenous and intracavitary GD2 CAR T had radiographic disease progression after intervention and the other five patients who received intravenous infusion alone had either partial response or stable disease. These three patients were also the only patients who required a second surgery for tumor resection [36▪]. Other recent trials have sought to further improve CAR T cell persistence and overcome the challenges of GBM tumor heterogeneity through testing bivalent CAR T cells delivered intrathecally. One of these includes the largest CAR T cell therapy trial in brain tumors to date, enrolling 92 patients with recurrent high-grade gliomas with most patients being rGBM (NCT02208362) [37]. This phase I trial evaluated interleukin (IL)-13Rα2-targeted CAR T cell infusions delivered via intratumoral, intraventricular, and dual intratumoral and intraventricular administration. There were no dose limiting toxicities noted across all groups [37]. mOS was significantly longer in the dual therapy group compared to all other groups (10.2 vs. 6.1 months, $P = 0.02$) [37]. Further phase I trials are ongoing in the pediatric population (NCT04510051), gliomas with leptomeningeal disease (NCT04661384), and in combination with nivolumab / ipilimumab (NCT04003649). Another approach is investigating bivalent CAR T cell therapy, which uses multiple T cell targets with the aim to address the issue of antigen escape. The interim analysis of the first in human phase I trial of EGFR-IL-13Rα2 CAR T cell therapy reported one patient with a dose limiting toxicity, and all 6 patients experiencing early, moderate to severe neuro-toxicity suggestive of immune effector cell associated neurotoxicity syndrome and tumor inflammation-associated neurotoxicity [38]. Thus far, size of tumor enhancement was reduced in all patients within 48 h of CAR T cell therapy administration; however, none were reduced by RANO criteria [38]. This trial is still ongoing with further phase I results pending (NCT05168423).

The latest CAR T clinical trial is a first in-human phase I trial evaluating CARv3-TEAM-E T cells, a novel EGFRvIII antigen specific CAR T cell with T-cell engaging antibody molecules (TEAM) (NCT05660369) [39▪▪]. CARv3-TEAM-E T cells were overall well tolerated by the three patients. Adverse events included encephalopathy and fatigue. In preliminary follow up, all three patients showed a decrease in radiographic contrast enhancement;

in two of the patients, there was an initial rapid decrease in radiographic enhancement within days of infusion with an increase in enhancement within a few months, which correlated with CARv3-TEAM-E T cell persistence. In the last patient, steady radiographic disease regression was seen at last follow up 5 months after infusion. Given the promising preliminary results, the study continues in phase I to determine optimal dosing.

Oncoviruses are thought to be immune activating by leveraging an implanted virus to infect and lyse tumor cells to activate an immune response against newly exposed tumor antigens. Recent advances in oncovirus research in the last few years have been considerable. A 2023 phase I clinical trial evaluated the safety of CAN-3110, an oncolytic herpes simplex virus (NCT03152318). The study included 41 rHGG and rGBM patients who underwent a single intralesional injection of CAN-3110, and found a significant correlation between HSV seropositivity and improved mOS (14.2 months in HSV seropositive vs. 7.8 months in HSV seronegative) [40]. Similarly interesting are results from the oncolytic measles virus, MV-CEA, with promising phase I results from a trial of 23 patients injected with MV-CEA intralesionally which was shown to be safe after multiple injections. mOS was 11.5 months [41].

Radiotherapy and radiosurgery

While the utility of radiation therapy in nGBM is widely accepted, its benefit in recurrence is not well characterized. Radiotherapy for rGBM with concurrent bevacizumab was shown to be safe and improve 6 month PFS compared to bevacizumab alone (54% vs. 29%, respectively, $P = 0.001$); however, there was no improvement in mOS (10.1 vs. 9.7 months, $P = 0.46$) [42]. In a separate study, border zone stereotactic radio surgery (BZ-SRS) was performed with bevacizumab compared to historical institutional controls and did not reveal a statistically significant improvement in mOS (11.73 months vs. 8.74 months, respectively; $P = 0.3$). Though not statistically significant and not compared to a trial specific control group, there was a trend towards improved OS. Limitations included small sample size and slow accrual [43].

CONCLUSION

Despite continued research into therapeutic approaches to improve outcomes for patients with GBM, progress has been modest. Adding new drugs to existing standard of care therapies has had a limited impact but multiple novel strategies are promising. Using focused ultrasound to improve drug delivery across the BBB, single and combination immunotherapy strategies including GBM-specific engineered CAR T cells and approaches to improve radiotherapy are cutting edge strategies to improve outcomes for GBM patients.

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Conflicts of interest

There are no conflicts of interest.

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