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Beyond Alkylating Agents for Gliomas: *Quo Vadimus?*

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OVERVIEW

Recent advances in therapies have yielded notable success in terms of improved survival in several cancers. However, such treatments have failed to improve outcome in patients with gliomas for whom surgery followed by radiation therapy and chemotherapy with alkylating agents remain the standard of care. Genetic and epigenetic studies have helped identify several alterations specific to gliomas. Attempts to target these altered pathways have been unsuccessful due to various factors, including tumor heterogeneity, adaptive resistance of tumor cells, and limitations of access across the blood-brain barrier. Novel therapies that circumvent such limitations have been the focus of intense study and include approaches such as immunotherapy, targeting of signaling hubs and metabolic pathways, and use of biologic agents. Immunotherapeutic approaches including tumor-targeted vaccines, immune checkpoint blockade, antibody-drug conjugates, and chimeric antigen receptor-expressing cell therapies are in various stages of clinical trials. Similarly, identification of key metabolic pathways or converging hubs of signaling pathways that are tumor specific have yielded novel targets for therapy of gliomas. In addition, the failure of conventional therapies against gliomas has led to a growing interest among patients in the use of alternative therapies, which in turn has necessitated developing evidence-based approaches to the application of such therapies in clinical studies. The development of these novel approaches bears potential for providing breakthroughs in treatment of more meaningful and improved outcomes for patients with gliomas.

The past decade has seen important breakthroughs in the treatment of newly diagnosed gliomas with the publication of mature and practice-changing results of several clinical trials. However, nearly all these trials have been based on the combination of radiation therapy and alkylating agents. The promise of targeted therapies, which has resulted in notable successes in several other cancers, has not been realized in patients with gliomas despite numerous trials of agents targeting the most common signaling pathways altered in these tumors.¹ Although ongoing studies are actively examining the mechanisms for the failure of targeted therapies in gliomas, alternative approaches that seek to attack tumor cells in ways that circumvent tumor resistance and heterogeneity are being increasingly explored. One of the more exciting of therapeutic strategies that has emerged in recent years involves immunotherapy involving a variety of methods including cell-free and cell-based vaccines,

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antibody-drug conjugates, and checkpoint blockade, which exploit the expression of tumor-specific antigens and neutralize tumor-mediated immunosuppression.² Another emerging area is the identification and targeting of tumor-specific metabolic and protein-processing pathways that act as hubs for converging cellular processes vital for tumor cell survival.³ Targeting such hubs has the potential to disable the complex signaling networks that tumor cells depend on for survival and resistance to therapy. However, the slow progress in developing effective therapies against gliomas has also resulted in patients seeking alternative and often untested therapies that are used concurrent with or as alternatives to standard therapy⁴; the rigorous assessment of such treatments through systematic studies is emerging as an equally important aspect of cancer care. The following sections examine the current state of these varied approaches and their impact on the treatment of patients with gliomas.

NEW APPROACHES TO GLIOMA THERAPY: TARGETED THERAPIES AND BEYOND

Current Standards of Care for Gliomas

Recent studies have established new standards of care for patients with gliomas. For adults with World Health Organization (WHO) grade II glioma after maximum safe resection, radiation therapy (RT) followed by chemotherapy using a combination of procarbazine, lomustine, and vincristine resulted in improvement of survival compared with RT alone, particularly for patients with low-grade oligodendroglioma.⁵ The same regimen also resulted in improved overall survival (OS) in patients with WHO grade III (anaplastic) oligodendrogliomas that had codeletions of chromosome 1p and 19q.^{6,7} Further characterization of this benefit is being explored in a randomized CODEL trial that seeks to compare the benefits of RT with procarbazine, lomustine, and vincristine with that of RT with temozolomide (TMZ) against 1p/19q codeleted anaplastic gliomas.⁸ The optimal standard of care for patients with anaplastic gliomas without 1p/19q codeletion is currently being explored in a multicenter CATNON trial that randomly assigned patients to four different treatment arms to assess the benefit of adding TMZ as adjuvant or concurrent therapy with RT. Recently reported interim results of this study indicated that the two arms with adjuvant TMZ had a better outcome compared with the two without.⁹ Based on these data, the trial has been modified to eliminate the arms without adjuvant TMZ and now continues with two arms (RT followed by TMZ vs. RT with TMZ followed by TMZ), the results of which are awaited. In the setting of recurrent grade II or grade III gliomas, there are no clear new standards of care; currently used treatments include reirradiation, alkylating agents, and treatment of secondary glioblastoma (GBM) with bevacizumab. Lastly, the current standard of care for adults up to age 70 with newly diagnosed GBM after maximum safe resection consists of chemoradiation therapy (6 weeks) with concurrent daily TMZ followed by up to six monthly cycles of adjuvant TMZ, which improved survival particularly in the subgroup of patients in whom tumors have promoter methylation of methyl-guanyl methyltransferase (*MGMT*).^{10,11} Efforts to intensify adjuvant TMZ dosing or to add bevacizumab to this regimen have failed to improve survival in this setting. However, recent data showed that the addition of low-intensity alternating electrical fields to the standard of care therapy along with adjuvant TMZ, using transducer arrays applied to the scalp for more

than 18 hours a day (tumor-treatment fields; Optune) improved OS in adults with newly diagnosed GBM independent of the *MGMT* promoter status.¹² In elderly patients, a shortened course of chemoradiotherapy (3 weeks) followed by up to 12 months of adjuvant TMZ was both tolerated and improved OS compared with RT alone.¹³ Treatments for recurrent GBM include bevacizumab, nitrosoureas, tumor-treatment fields, and several other chemotherapeutic agents that are currently less frequently used given their limited benefit. None of these treatments have provided a survival benefit, although bevacizumab received regulatory approval based on response rate and improved progression-free survival (PFS).^{14,15}

Targeted Therapies Against Gliomas: Rationale and Limitations

Extensive genetic, epigenetic, and molecular studies have been conducted to delineate the key signaling pathways and alterations in gliomas.^{16–20} Early studies had identified key roles for three major pathways in gliomagenesis and progression including (1) the receptor tyrosine kinase/phosphoinositide 3-kinase (PI3K)/Akt pathway, including alterations in *EGFR*, *Her2*, *PDGFR*, *FGFR*, and *cMET* (approximately 90%), (2) the p53 pathway including alterations in *TP53*, *MDM2*, and *MDM4* (approximately 85%), and (3) the Rb and cell cycle–related pathways including defects in *RB*, *CDKN*, *CDK*, and cyclins (approximately 80%).¹⁶ More in-depth analysis has revealed the striking complexity of genetic and epigenetic changes in both low- and high-grade gliomas.^{19,20} These data provided strong rationale for several clinical trials targeting key GBM relevant pathways, especially those of receptor tyrosine kinase inhibitors initially in the setting of recurrent GBM and subsequently in the newly diagnosed setting; however, it was soon evident that single-agent trials of these agents were largely ineffective in providing benefit in either PFS or OS for this patient population.^{21–23} Focusing on the strategy of overcoming bypass pathways that the tumor cells deploy to establish resistance to the action of single agents, combination strategies targeting multiple pathways were subsequently tried but were again strikingly unsuccessful in providing an improvement in outcome.²⁴ These results point to limitations in our understanding of the complexity of survival and resistance mechanisms adopted by glioma cells and the need for more concerted effort to delineate the adaptive mechanisms of these cells that can be new targets for therapy.

Recent Advances in Understanding the Biology of Gliomas

In-depth genetic and epigenetic analyses of large numbers of low- and high-grade gliomas have recently yielded novel insights into the complexity of the alterations in these tumors.²⁵ From a clinical perspective, this has also provided evidence that histologic diagnosis may not accurately correlate with outcome; this has led to a revision of the WHO classification of brain tumors with modifications that allow incorporation of such molecular markers into conventional diagnostic approaches to align better with clinical outcome.²⁶ Although some of these markers have shown potential to be predictive markers that can help selection of treatment options, most are prognostic in nature and inform largely of the intrinsic behavior of the tumors without specificity to the treatments used.^{6,7,11,27–29} From the perspective of the basic biology of the tumors, the studies have shown that tumor heterogeneity is one of the most critical factors that dictates tumor behavior. Such heterogeneity is seen to be not only spatial (with different regions of the same glioma evolving along distinct pathways) but

also temporal (with emergence of new mutations and hence biologic behavior with tumor treatment and progression).^{30–32} It is also becoming clear that treatments can induce mutations that can contribute to clonal evolution of gliomas.³³ Such heterogeneity has provided an explanation for why therapies targeting single or even multiple pathways in gliomas fail to uniformly affect the majority of tumor cells or eliminate emergent clones during the course of tumor growth and therapy.

Emergent Targets for Antiglioma Therapies

Novel therapies for gliomas must overcome tumor heterogeneity and disable resistance mechanisms to treatment to be effective in improving outcome. The search for such strategies has resulted in the identification of novel targets that promise to change conventional approaches and are in advanced clinical studies or in early stages of investigations. Immunotherapy has emerged as one of the most promising strategies against gliomas currently in clinical trials and is aimed at either disabling immunosuppression induced by tumor cells or enable tumor targeting of immune cells by identification of overexpressed proteins or neoantigens. Several other emerging areas that bear promise to change therapeutic outcome of patients include targeting signaling hubs, use of biologic agents, disabling tumor-specific metabolic pathways, and activating death pathways that can eliminate tumor cells independent of internal tumor heterogeneity. The following sections briefly review these approaches and outline ongoing or potential clinical trial strategies related to these approaches.

The high frequency (approximately 80%) of mutations in isocitrate dehydrogenase 1 (*IDH1*) in WHO grade II and III gliomas as well as secondary GBM³⁴ associated with increased levels of 2-hydroxyglutarate (2HG), a putative oncometabolite that is believed to drive gliomagenesis,³⁵ has provided a strong rationale for targeting mutant IDH1 as a therapy against gliomas³⁶; this has led to development of pharmacologic inhibitors of IDH1 that are currently in early clinical trials. A phase II trial of IDH-305, a selective R132H-IDH1 inhibitor against progressive WHO grade II and III gliomas, is due to open shortly (NCT02977689). Another trial aimed at low-grade gliomas that have high 2HG as measured by magnetic resonance spectroscopy proposes to assess changes in 2HG in tumor tissue and clinical outcome in terms of tumor response (NCT02987010). Another agent, AGI-5198, was shown to inhibit the ability of mutant IDH1 to produce 2HG in glioma cells, suggesting a potential for clinical activity in these tumors.³⁷

Tumor cells including glioma cells, unlike normal cells, when subject to hypoxic environments, preferentially continue to use the anaerobic tricarboxylic acid cycle even after normoxic conditions are restored, the so-called Warburg effect.³ Hypoxic regions are a key feature of GBMs and associated with areas of pseudopallisading necrosis, which also show increased expression of hypoxia-inducible factor α (HIF1 α), a key player in inducing the Warburg effect.³⁸ HIF1 α is stabilized in the setting of hypoxia and acts as a transcription factor that triggers a number of changes in gene expression and protein signaling aimed at increasing levels of tumor cell defense mechanisms include resistance pathways, accelerated metabolism, and angiogenic factors.³⁹ Therapeutic agents that target upstream effectors that stabilize HIF1 α such as PI3K and mTOR have failed to yield substantial responses or

improved outcome in early trials, likely because of activation of bypass pathways. Agents that directly target HIF1 α have been tested in early trials, but data regarding their efficacy have not been promising.³⁹ More recently, the identification of phosphokinase M2 (PKM2) as being highly expressed in cancers, being transcriptionally upregulated by HIF1 α , and promoting the Warburg effect,^{40,41} has triggered efforts to develop PKM2 inhibitors as anticancer agents.^{42,43} Depletion of PKM2 in cancer cells reverses the Warburg effect and inhibits tumor formation, providing a strong rationale for targeting PKM2 to inhibit cancer metabolism and tumor growth. Novel inhibitors to inhibit PKM2 are currently under development and may provide a novel therapeutic option against GBM (Fig. 1).^{42,43}

Targeting basic cellular processes common to oncogenic pathways could potentially disable resistance mechanisms deployed by GBM cells and overcome the effect of heterogeneity. Heat shock response is one such highly conserved process that protects cells against adverse environmental stresses (e.g., oxidative stress, acidosis, or metabolic stress).⁴⁴ Heat shock response is mediated by the heat shock protein (HSP) family, which directs protein folding, oligomerization, and secretion, enabling the cell to generate potent resistance and survival mechanisms. Hsp90, a key member of this family, regulates folding and stabilization of several oncoproteins and is overexpressed in cancer cells; a high-affinity form of the protein is specifically expressed by cancer cells, allowing them to rapidly process proteins unlike normal cells.⁴⁵ Targeting Hsp90 can destabilize client oncoproteins, leading to their proteosomal degradation disabling crucial defense mechanisms used by GBM and sensitizing them to treatment.⁴⁶ Several Hsp90 inhibitors that block ATPase activity in a tumor-selective manner are in clinical trials.⁴⁷ Their use against GBM has been limited due to their inability to cross the blood-brain barrier, short duration of action, or unacceptable toxicity profile.⁴⁸ Second-generation Hsp90 inhibitors such as AUY922,⁴⁹ Onalespib,^{50,51} and Debio0932,⁵² some of which cross the blood-brain barrier, are currently in clinical trials against cancer and being considered for clinical trials against gliomas.

Another central regulator of protein processing involves the unfolded protein response (UPR), which is an evolutionally conserved central defense mechanism activated when protein that protects allows cells to adapt to endoplasmic reticulum (ER) stress.⁵³ ER stress results in the incorrect folding and improper glycosylation of newly synthesized proteins. UPR allows cells to re-establish homeostasis by inducing a cell cycle arrest and blocking of protein translation, which prevents new protein formation during the period of ER stress.⁵³ Cancer cells including glioma cells are frequently subject to hypoxia and nutrient deprivation triggering tumor-specific ER stress, as a result of which they become highly reliant on the UPR for survival, making it an ideal target for therapeutic targeting.⁵⁴ Given that the UPR has also emerged as a mechanism for resistance to conventional therapies in solid tumors,⁵⁵ inhibitors of the UPR may serve to overcome resistance to standard antiglioma treatments and enhance their antitumor efficacy. The UPR is mediated by the dissociation of GRP78 from its inhibitory association with three transducer proteins—protein kinase R-like ER kinase, inositol-requiring enzyme 1, or activating transcription factor 6—allowing it to bind to and chaperone unfolded proteins.⁵⁵ Once released, protein kinase R-like ER kinase, inositol-requiring enzyme 1, or activating transcription factor 6 initiate downstream signals that cause transcriptional arrest and assist in alleviating ER stress. Inhibitors of GRP78 can disrupt signaling through the UPR, facilitate the reversal of

ER, and consequently sensitize tumor cells to conventional treatments. AR-12, a novel orally bioavailable agent, has been reported to downregulate GRP78 and affect the UPR.⁵⁶ Inhibitors of the mitogen-activated protein kinase/extracellular signal-regulated kinase pathways also decrease levels of GRP78 and can potentially inhibit the UPR. Novel inhibitors of GRP78 pathway are in continued development, and these agents are expected to enter clinical trials.⁵⁷

Several novel and unconventional agents are currently entering clinical trials that have shown promising preclinical data against gliomas. BXQ-950 is a first-in-class agent that is a lipid-protein complex composed of Saposin C (SapC), a lysosomal protein, and a phospholipid (dioleoylphosphatidylserine [DOPS]) assembled into nanovesicles (SapC-DOPS), which selectively kill tumor cells through targeting of phosphatidylserine on the cancer cell surface, activating the ceramide cell death pathway as demonstrated in recent preclinical studies in gliomas.⁵⁸ The agent is currently in a first-in-human phase I trial including in patients with recurrent GBM (NCT02859857). G-202 (mipsagargin) is another novel prodrug that is activated by prostate-specific membrane antigen, which is expressed by GBM and tumor-associated vasculature but not in normal tissue, and is currently in phase II trials against recurrent GBM (NCT02876003 and NCT02067156). Glioma stem cells have also been assessed as novel targets in GBM; BBI608 (napabucasin), an orally bioavailable STAT3 inhibitor that targets cancer stem cells,⁵⁹ is currently in a phase I/II trial against recurrent GBM in combination with TMZ (NCT02315534).

IMMUNOTHERAPY FOR GLIOMA

Immunotherapy has emerged as one of the most exciting of therapeutic strategies against gliomas with a variety of approaches that harness the recent insights gained into cell based and humoral immune responses against cancer. The following section outlines several key strategies and associated ongoing clinical trials including a summary or early results available to date (Table 1).

Checkpoint Inhibitors

Checkpoint inhibitors (CPIs) work by interacting with molecules involved in the normal immune-inhibitory pathways of the body, tasked with limiting immune responses and avoidance of autoimmune reactivity.⁶⁰ A phase III trial (Checkmate 143; NCT02017717) is underway, looking at treatment of patients with recurrent GBM with nivolumab, a PD-1 inhibitor, and ipilimumab, a CTLA-4 inhibitor.⁶¹ Preliminary data for this trial showed 90% of patients receiving a combination of nivolumab and ipilimumab having grade 3 or 4 adverse events in response to treatment. Preliminary efficacy results showed a 12-month OS of 40% for nivolumab (3 mg/kg), 30% for nivolumab (1 mg/kg) plus ipilimumab (3 mg/kg), and 25% for nivolumab (3 mg/kg) plus ipilimumab (1 mg/kg). Another phase III trial (Checkmate 498; NCT02617589) is investigating treatment with nivolumab combined with RT in adults with newly diagnosed MGMT promoter unmethylated GBM compared with standard therapy. KEYNOTE-028 is a phase I trial looking at the use of pembrolizumab (PD-1 inhibitor) for solid tumors and includes a GBM cohort of 26 patients.⁶² A total of 73.1% of patients experienced treatment-related adverse events, with 15.4% experiencing

grade 3 or 4 adverse events. One patient exhibited a partial response to treatment, whereas 12 patients exhibited stable disease. Results regarding PFS and OS did not show noteworthy improvements from current standard therapy. Additional studies are underway. The relatively modest effect of CPIs in trials to date may be because of the fact that GBM is not generally primed for immune response. Future studies using CPIs in combination therapies that may increase the degree of immune activity against GBM cells may provide better outcomes.

T-Cell Therapies

Adoptive T-cell therapy is a novel approach to glioma immunotherapy that allows the targeting of treatment to a patient's specific tumor-associated antigen (TAA) profile, thus limiting the off-target effect to surrounding nonmalignant cells. Autologous lymphocytes are harvested and grown ex vivo, allowing for modification and recognition of specific TAAs prior to implantation in the patient.^{64,65} Another novel approach uses chimeric antigen receptor (CAR) T cells, which uses autologous T-cell extraction and transduction to express modified tumor antigen T-cell receptors on the cell surface, allowing for chimeric T-cell activation independent of surface major histocompatibility complexes.⁶⁶ Brown et al⁶⁷ recently published a case report of one patient involved in a phase I trial (NCT02208362), treating patients with recurrent GBM using CAR T-cells targeting the TAA interleukin-13 receptor alpha 2 (IL-13R α 2). The patient exhibited tumor regression from 70%–100% in all lesions, an effect that was maintained for 7.5 months. Furthermore, this group reported 10 patients currently undergoing treatment, with minimal side effects, and CAR T cells detected in cerebrospinal fluid or tumor cyst fluid for more than 7 days.⁶⁸ These findings suggest that CAR T cells may be well tolerated by patients and are capable of producing a relevant treatment response in vivo. Other early-stage CAR T-cell trials include NCT01454596 (National Cancer Institute), treating patients in whom GBM expresses EGFR type III (EGFRvIII), a known tumor-specific antigen, and NCT01109095, testing the safety of CAR T cells targeting HER2, a tumor-specific antigen expressed on 87% of GBM cells.^{69,70} For this second study, the gene expressing the HER2 antibody was transduced into T cells selected for their reactivity to cytomegalovirus (CMV), postulating that these cells would be more reactive as they would respond to both tumor cells and CMV, a viral antigen found in many patients with GBM.

Peptide Vaccine Therapies

Vaccination strategies for GBM are aimed at creating vaccines targeting specific tumor antigens, such as EGFRvIII and isocitrate dehydrogenase 1 (IDH1).^{60,66,71} The ACT III trial was a phase II trial of newly diagnosed patients with GBM treated with rindopepimut (CDX-110), a vaccine targeting EGFRvIII. Early results showed a survival benefit, with patients exhibiting a PFS at 5.5 months of 66% and median OS of 21.8 months.⁷² However, the phase III trial (ACT IV) was terminated early when it failed to show a survival benefit.⁷³ It has been speculated that the results may have been influenced by the patients in the control arm faring better than would be expected of typical control subjects with GBM.^{66,73} Reardon et al⁷⁴ reported the results of a phase I/II trial of SL-107, a peptide vaccine targeting three tumor antigens— IL-13R α 2, Ephrin A2 (EphA2), and Survivin—in patients with recurrent GBM. Early results showed a partial response in one patient (more than 33

weeks in duration) and stable disease in 15 patients (median duration 8 weeks). Migliorini and Dutoit⁷⁵ reported results of a trial using IMA950, a peptide vaccine composed of 11 tumor-specific peptides.⁶⁶ For the six patients treated under the initial protocol, median OS was 17.5 months (range 11–21 months). Another target of interest under investigation for potential vaccination therapy is HSP.^{76,77} A phase II trial (NCT01814813) is evaluating heat shock protein–peptide complex 96 (HSPPC96) with bevacizumab in patients with recurrent glioma. Similarly, IDH1 is a novel target for vaccine therapy, with one phase I trial in patients with grade III/IV glioma testing an IDH1 vaccine (NOA-16; NCT02454634).

Dendritic Cell Therapies

Dendritic cell (DC) therapies function by harvesting DCs from the patient and exposing them to the tumor-specific peptides or tumor lysate ex vivo, prior to being injected back into the patient.^{5,18} Previous clinical trials using DC therapy have shown encouraging results, with improvement in OS and 2-year survival compared with the current therapy.⁶⁰ Santos et al⁷⁸ published data from a phase II (NCT01280552) trial using ICT-107, a DC vaccine encompassing autologous DCs incubated ex vivo with six tumor-specific peptides. The data showed a relationship between HLA-A2–positive patients and an immune response to treatment, associated with both OS and PFS. The Mayo Clinic group reported a trial (MC1272; NCT01957956) of DC therapy in patients with newly diagnosed GBM.⁷⁹ Autologous DCs were pulsed with allogenic tumor lysate from two human GBM cell lines. Mean follow-up was roughly 1 year (range 0.19–1.77), with 80% OS. The University of California, Los Angeles group reported recently on a phase IIa trial (NCT01635283) of DC therapy in patients with grade II glioma treated with autologous DCs pulsed with autologous tumor lysate.⁸⁰ No difference was noted in time to progression between study patients and a matched cohort. One phase III trial (NCT00045968) using a tumor-lysate pulsed DC vaccine (DCVax-L) was recently completed in December 2016 with results not yet reported.

Oncolytic Viral Therapies

Oncolytic virus therapy uses genetically modified viral vectors that have the ability to both directly attack malignant cells as well as produce a durable host immune response to them.^{81,82} NCT00390299 is a phase I trial for patients with recurrent GBM, assessing the safety and efficacy of measles virus transfected with human carcinoembryonic antigen as a marker for replication in vivo.⁶⁶ The PVSRIPO trial (NCT01491893) is evaluating a recombinant poliovirus (PVSRIPO) and has shown promising early results.^{83,84} Patel et al⁸⁵ recently reported on a new clinical trial using a recombinant oncolytic herpes simplex virus that functions through direct oncolytic action against malignant cells and transfection of a viral payload causing malignant cells to secrete IL-12. Tejada et al⁸⁶ reported preliminary results from a phase I trial (NCT01956734) using an oncolytic adenovirus (DNX-2401) and TMZ with noteworthy results: one patient alive 30 months after treatment with no evidence of progression and two further patients alive at 23 months. Aghi et al⁸⁷ also reported the preliminary results of three phase I trials using replicating retrovirus Toca 511 in patients with recurrent GBM, delivered via three distinct methods. Toca 511 is a recombinant retrovirus that transfects yeast cytosine deaminase into malignant cells, allowing for subsequent treatments with Toca FC (a 5-fluorocytosine derivative) to convert to 5-

fluorouracil within the malignant cells.^{87,88} Median OS for all three trial groups was 12.1–13.6 months.

Combination Immunotherapy Approaches

Several trials are investigating the use of combinations of immunologic agents to elicit the synergistic effects of such therapies. These include the CAPTIVE trial (NCT02798406), a phase 2 trial combining pembrolizumab with DNX-2401 (oncolytic adenovirus), the AVERT trial (NCT02529072), a phase I trial testing a combination of nivolumab and a DC vaccine (pp65) against recurrent glioma, a phase I/II trial (NCT02423343) for several solid malignancies, including recurrent GBM, testing nivolumab in conjunction with galunisertib, a transforming growth factor-beta receptor I kinase inhibitor, and a trial (NCT03018288) using pembrolizumab in conjunction with HSPPC96, an HSP peptide vaccine. Further research is likely needed to understand the critical interplay of immunosuppressive mechanisms within GBM, but combination trials such as these will hopefully provide us with useful information regarding concurrent immunotherapy treatments.

INTEGRATIVE MEDICINE AND ALTERNATIVE THERAPIES AGAINST GLIOMAS

Scope and Definition of Integrative Medicine

Integrative medicine, a new name for an ancient field of medicine, was previously known as alternative medicine, but because the term “alternative” implies in lieu of traditional medical therapy, the name has been recently been changed to the more inclusive name. Practitioners in oncology often encounter patients seeking advice about integrative oncology practices but whom are often ill equipped to address such questions, which may result in minimizing or avoidance of discussion regarding these queries. This common practice could lead to the patients becoming reluctant to discuss such therapies with their clinical team and potentially withholding information about the integrative techniques that they may be using. It is noted that up to 65% of cancer survivors report using integrative medicine practices at some time during their clinical course,⁸⁹ making it a highly relevant issue in the management of oncology patients. It has hence become important for practitioners in oncology to address this issue, encourage a discussion with the patients related to integrative therapy, and provide evidence-based information to help them make appropriate choices. Although reducing the potential for unreported use of integrative medicines by patients and encouraging open dialogue is a major reason for practitioners to educate themselves about integrative medicine, there are also evidence-based practices that demonstrate not only improvement in quality of life measures but also an increase in OS and PFS in patients with cancer.

Role of Stress and Mitigation of Stress

Stress and stress reduction is one of the most difficult fields to study in medicine because of often-subjective measures but is also the most interesting of all integrative medicine fields. Thaker et al⁹⁰ used a validated stress model to test the hypothesis that stress can induce tumorigenesis through stimulation of the B-adrenergic receptor on tumor cells. Nude mice were placed in a stress-inducing restraint system, and human ovarian carcinoma cells were

inoculated into the peritoneal cavity. As compared with the control nonstressed mice, the ovarian cancer cells grew by up to 275% in the stressed-out mice. The pathophysiology of this response is poorly understood but is thought to be secondary to stimulation of the B-adrenergic receptor on tumor cells and transcriptional upregulation of VEGF. A legitimate question hence is whether decreasing stress can cause a decrease in tumor burden and improve survival. In this context, a randomized trial showed a considerable survival benefit of stress reduction in patients with metastatic breast cancer.⁹¹ Patients undergoing adjuvant breast cancer therapy were randomized to an intervention arm that taught strategies to “reduce stress, improve mood, and alter health behaviors” for 1 year (26 sessions). At 11 years of follow-up, there was a striking improvement in median survival in the intervention arm (6.1 years) versus the assessment-only arm (4.8 years). Multivariate analyses confirmed that patients randomized to the intervention arm had a significantly lower risk of death because of breast cancer (hazard ratio 0.44; $p = .016$). Although there is a paucity of such trials, the importance of mental health in patients with cancer, often minimized in routine care, has been shown to improve quality of life measures and now even survival in a statistically meaningful way. Incorporating stress reduction techniques such meditation, psychologic therapy, and psychiatric intervention to address issues such as anxiety and depression into routine oncological clinical practice hence must be an integral part of the management of the patient with cancer in a modern era of medicine.

Exercise and Its Impact on Cancer

All areas of medicine accept that regular exercise is important for maintaining mental and physical health, but the question of whether exercise can actually affect cancer growth has only recently been systematically addressed. In a laboratory study, mice were randomized to a cage with a wheel for running or into a cage without a wheel, and mice in both groups were inoculated with B16F10 melanoma cells. Strikingly, after 4 weeks of running, the exercise mice had a 61% ($p < .01$) reduction in tumor as compared with the mice that were not exercising. Exercised mice had increased natural killer cell mobilization that was believed to be the pathophysiology due to which tumor progression was decreased.⁹² In an era of immunotherapy, these data suggest that exercise may have an important part in therapy.

Primary brain tumors such as high-grade gliomas are highly aggressive and treatment resistant. A very interesting trial examined the role of exercise in patients with recurrent grade III and grade IV malignant gliomas in which 243 patients with a Karnofsky performance status 70 or higher were prospectively given a self-administered questionnaire that assessed exercise behavior and performed a 6-minute walk test to assess functional capacity.⁹³ Exercise was an independent predictor of survival ($p = .0081$), although, interestingly, functional capacity was not. Exercise was also a better predictor of survival than Karnofsky performance status, age, sex, grade, and number of prior progressions. The adjusted hazard ratio mortality was 0.64 (95% CI, 0.46–0.91) for patients reporting strenuous exercise. That strenuous exercise was an independent predictor of survival is a striking finding in an extremely treatment-resistant tumor given that to date, no chemotherapy, radiation therapy, nor surgical therapy have been shown to improve survival in a meaningful way in recurrent high-grade gliomas. Patients often stop exercising after the

diagnosis of cancer because of several factors, including fatigue and concerns regarding the impact of physical exercise on their fragile health status, an attitude that may be inadvertently encouraged by clinicians. The data presented above and in many animal models point to the contrary and suggest that patients should continue to exercise as vigorously as possible not only to maintain performance status but also for its potential effect on controlling tumor growth and improving survival.

Diet and Nutrition

One of the most controversial areas of integrative oncology is related to diet and nutrition and its effect on cancer. There are often concerns about weight loss and poor protein intake in patients with a hypermetabolic state. The prevalent belief among clinicians that diet has no notable effect on tumors has been challenged by emerging data in animals as well as humans. This is highlighted by the intriguing results of a randomized, double-blinded, placebo-controlled study assessing the role of flax seed in postmenopausal patients with breast cancer conducted by Thompson et al.⁹⁴ After initial biopsy, patients were randomized to a diet taking 25 grams of flaxseed daily in a muffin versus one with no flaxseed and with no other changes in their regular diets. At the time of lumpectomy, the flaxseed arm was found to have a considerable decrease (median 34.2%) in Ki-67 labeling index and considerable increase in apoptotic index (30.7%). No quantifiable changes on these indices were noted in the placebo group. Other similar studies have shown that even small changes in diet for a short period of time can induce changes at a cellular level. However, the question of whether diet can change tumorigenesis in a clinically meaningful way has been challenging to answer because of the difficulties in evaluating the effect of diet in an evidenced-based manner. Randomized controlled trials are virtually impossible, and so clinicians have to often rely on retrospective trial data, which are fraught with statistical bias. One large randomized control trial, the PREDIMED study, conducted in Spain on 4,282 women age 60 to 80 at high cardiovascular risk, showed compelling results in this context. These subjects were randomized to a Mediterranean diet with olive oil, a Mediterranean diet with nuts, or a low-fat control diet and monitored for development of breast cancer. There were 35 cases of breast cancer in a median follow-up of 4.8 years; intriguingly, the multivariable-adjusted hazard ratios for the Mediterranean diet plus olive oil group versus the control group was 0.32 (95% CI, 0.13–0.79).⁹⁵ The impact of these results can be considered in the context that a chemotherapy agent that showed similar results in preventing breast cancer would have been considered highly successful.

Other specialties in medicine such as cardiology have willingly embraced the impact of stress reduction, exercise, and diet in the prevention and treatment of disease. In oncology, such acceptance has lagged behind despite cumulative data that support the direct beneficial effects of such modalities on quality of life and survival. The reasons for the resistance in accepting the value of such measures in the therapeutic strategies against cancer are unclear. It can be speculated that this may be due to the lack of a direct and verifiable logical link between cancer and, for instance, exercise. It is also possible that the lack of conventionally accepted evidence based on robust clinical trials raise skepticism about the results of small uncontrolled studies or anecdotal experience. Further, in the era of highly specific and targeted therapies, it is possible that the role of a broader and less specific intervention such

as diet or exercise may have lesser acceptance as a legitimate anticancer therapy. Perhaps clinicians also have concerns that patients may choose integrative practices in lieu of traditional medical therapy with potential medical consequences. Equally likely, however, is that clinicians trained in oncology receive little or no training in aspects of integrative medicine given the traditional stigma and biases associated with this field in traditional training programs as being a nonspecific science. However, it is highly encouraging that Integrative Oncology as a field is moving forward and that there is a growing recognition of the obligation in clinicians to familiarize themselves with the fundamentals of this field and to critically examine the evidence in the field as well as generate carefully designed studies, including through new study designs and clinical trial approaches to provide evidence-based results on which practice can be based. This is imperative for the benefit of our patients who are currently bombarded with nonevidence-based recommendations from a variety of nonmedical sources, including the internet and social media, every day.

CONCLUSION AND FUTURE DIRECTIONS

Recent advances in treatment have yielded incremental improvement in the outcomes of patients with gliomas; however, paradigm-shifting therapies that provide considerable prolongation of survival and improvement in quality of life for these patients have been elusive. The need for unconventional approaches to targeting gliomas has led investigators to explore targets and strategies that go beyond traditional chemotherapeutic agents, including the ones outlined in the sections above. A variety of other strategies, including gene editing, noncoding RNAs, biologic therapies including viral and nonviral vectors, in addition to cell-based therapies, heat-based therapies, novel surgical techniques, and local delivery using blood-brain barrier disruption and convention-enhanced deliveries, as well as novel approaches with radiation therapy techniques, are under development. An exhaustive coverage of these techniques is outside the scope of this review, but it is recognized that these equally cutting-edge approaches are under active study. These novel strategies bear great promise in providing the long overdue improvement in quality of life and survival for patients with gliomas.

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KEY POINTS

- Alkylating therapies remain the cornerstone of standard-of-care therapy for gliomas despite advances.
- Identification and targeting of specific signaling pathways most commonly altered in gliomas have failed to yield improvement in outcomes in patients with these tumors.
- There is urgent need for a broader targeting of the diverse pathways that mediate adaptive resistance to treatment and facilitate tumor recurrence.
- Novel strategies include immunotherapeutic approaches, targeting of metabolic pathways, and harnessing of newer insights into the biology of gliomas.
- Additionally, the lack of curative therapies for gliomas has also increasingly encouraged patients to use alternative therapies with little scientific support. Critical assessment and systematic study of such treatment options is essential for providing the best care for patients with gliomas.

FIGURE 1. Metabolic Pathways Active in GBM Involving Enzymes of Glycolysis, the Pentose Phosphate Pathway, Fatty Acid and Glutamine Metabolism, and Their Regulation by Known Oncogenes and Tumor Suppressor Genes in Proliferating Cells

Growth factor/PI3K/AKT signaling stimulates glucose uptake and flux through the early part of glycolysis. Tyrosine kinase signaling negatively regulates flux through at PKM2, making glycolytic intermediates available for macromolecular synthesis. Myc has been found to promote glutamine metabolism and inhibit oxidative metabolism by activating pyruvate dehydrogenase kinase (PDK). p53 decreases metabolic flux through glycolysis in response to cell stress.

Abbreviations: Acetyl-CoA, acetyl coenzyme A; ACL, ATP citrate lyase; AMPK, 5' adenosine monophosphate-activated protein kinase; DCA, dichloroacetate; FBP, fructose 1,6-bisphosphate; NADP, nicotinamide adenine dinucleotide phosphate; NADPH, reduced form of nicotinamide adenine dinucleotide phosphate; PDH, pyruvate dehydrogenase; PEP, phosphoenolpyruvate.

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TABLE 1

Active Clinical Trials for Immunotherapy in Glioma

Intervention (Target/Origin)	Phase	Population	Design	Estimated Primary Completion Date	NCT Identification
Peptide Vaccines					
IMA950 (multiple tumor antigens)	I/II	Newly diagnosed GBM	Open-label, single-group assignment	March 2016	NCT02343406
PEPDHIM (IDH1)	I	Recurrent grade II glioma	Open-label, single-group assignment	May 2017	NCT02193347
IDH1 peptide vaccine (IDH IR132H)	I	Grade III/IV glioma	Open-label, single-group assignment	August 2018	NCT02454634
HSPPC-96 (heat shock protein)	II	Recurrent GBM	Randomized, open-label, parallel assignment	July 2017	NCT01814813
DC Therapies					
ICT-107 (allogenic TAAs)	III	Newly diagnosed GBM	Randomized, double-blind, parallel assignment	December 2019	NCT02546102
DC vaccine (allogenic tumor lysate)	I	Newly diagnosed or recurrent GBM	Nonrandomized, open-label, parallel assignment	October 2018	NCT02010606
DC vaccine (autologous tumor lysate)	Pilot	Newly diagnosed GBM	Open-label, single-group assignment	November 2016	NCT01957956
DC vaccine (tumor lysate)	I	Recurrent GBM	Nonrandomized, open-label, parallel assignment	July 2018	NCT01808820
Human CMV pp65-LAMP mRNA-pulsed DC vaccine	II	Newly diagnosed GBM	Randomized, double-blind, parallel assignment	March 2019	NCT02366728
ICT-121 (CD 133)	I	Recurrent GBM	Open-label, single-group assignment	November 2017	NCT02049489
DCVax-L (autologous tumor lysate)	III	Newly diagnosed GBM	Randomized, double-blind, parallel assignment	November 2016	NCT00045968
CPIs					
Pembrolizumab (PD-1 inhibitor)	I	Solid tumors (Recurrent GBM)	Open-label, single-group assignment	August 2017	NCT02054806
Nivolumab (PD-1 inhibitor) with/without ipilimumab (CTLA-4 inhibitor)	III	Recurrent GBM	Randomized, open-label, parallel assignment	February 2017	NCT02017717
Durvalumab (PD-1 Inhibitor)	II	Newly diagnosed or recurrent GBM	Nonrandomized, open-label, parallel assignment	July 2017	NCT02336165
Pembrolizumab	II	Recurrent GBM	Randomized, open-label, parallel assignment	August 2016	NCT02337491
Nivolumab	III	Newly diagnosed GBM	Randomized, open-label, parallel assignment	March 2019	NCT02617589
Indoximod (IDO inhibitor)	I/II	Recurrent GBM	Nonrandomized, open-label, parallel assignment	December 2016	NCT02052648
T-Cell Therapies					
Genetically modified T cells (IL-13Ra2)	I	Recurrent GBM	Nonrandomized, open-label, parallel assignment	December 2018	NCT02208362
CAR T cells (EGFRvIII)	I/II	Recurrent GBM	Nonrandomized, single-group	December 2018	NCT01454596
CAR T cells (CMV, HER2)	I	Recurrent GBM	Open-label, single-group assignment	June 2014	NCT01109095

Intervention (Target/Origin)	Phase	Population	Design	Estimated Primary Completion Date	NCT Identification
CAR T cells (EphA2)	I/II	Newly diagnosed or recurrent GBM	Randomized, open-label, parallel assignment	September 2016	NCT02575261
Viral Therapy					
MV-CEA (measles virus)	I	Recurrent GBM	Nonrandomized, open-label, parallel assignment	June 2017	NCT00390299
PV/SRIPO (poliovirus)	I	Recurrent GBM	Open-label, single-group assignment	January 2017	NCT01491893
DNX2401 (adenovirus)	I	Recurrent GBM	Open-label, single-group assignment	December 2015	NCT01956734
Toca 511 (retrovirus) + Toca FC	II/III	Recurrent GBM	Randomized, open-label, parallel assignment	November 2017	NCT02414165
Combination Therapy					
DNX2401 + pembrolizumab	II	Recurrent GBM	Open-label, single-group assignment	December 2019	NCT02798406
DC vaccine + nivolumab	I	Recurrent GBM	Randomized, open-label, parallel assignment	May 2018	NCT02529072
Nivolumab + galunisertib (TGF- β RIK inhibitor)	I/II	Refractory solid tumors (recurrent GBM)	Nonrandomized, single group, open label	April 2018	NCT02423343
Pembrolizumab + HSPC-96	II	Newly diagnosed GBM	Randomized, parallel assignment	May 2018	NCT03018288

Abbreviations: NCT, National Clinical Trial; GBM, glioblastoma; DC, dendritic cell; TAAs, tumor-associated antigens; CPIs, checkpoint inhibitors; IDO, indoleamine 2,3-dioxygenase; CAR, chimeric antigen receptor; CEA, carcinoembryonic antigen; TGF, transforming growth factor.

Data derived from <https://clinicaltrials.gov>.