Scientific and Clinical Challenges within Neuro-Oncology

Marissa Barbaro, Howard A. Fine, Rajiv S. Magge

Both primary and metastatic brain tumors carry poor prognoses despite modern advances in medical therapy, radiation therapy, and surgical techniques. Gliomas, including glioblastoma (GBM), are particularly difficult to treat, and high-grade gliomas have poor outcomes. Treatment of brain tumors involves a unique set of scientific and clinical challenges, which are often not present in the treatment of systemic malignancies. With respect to scientific challenges, the anatomy and physiology of brain tumors (including the blood-brain barrier, blood-tumor barrier, and blood–cerebrospinal fluid barrier) prevent adequate drug delivery into the central nervous system. The unique nature of the immune system in the central nervous system as well as the immunosuppressive microenvironment of tumors such as GBM also create therapeutic roadblocks in the treatment of brain tumors. Tumor heterogeneity, particularly in GBM, has classically been believed to contribute to multitherapy resistance; however, recent data suggest that this may not be the case. Clinical challenges include neurologic and medical comorbidities of patients with brain tumor, as well as potential toxicity of tumor-directed treatment. Clinical trials investigating new treatment paradigms are needed, but several roadblocks exist to good and promising clinical trial availability.

INTRODUCTION

Brain tumors, including primary brain tumors such as gliomas as well as brain metastases, have proved difficult to treat. Prognoses for many brain tumors remain poor. Glioblastoma (GBM) in particular is uniformly fatal, with a median survival of approximately 14.6 months even with standard treatment with radiation and temozolomide.[1] Substantial advances have been made in the treatment of systemic malignancies, especially with the development of immunotherapies and targeted agents aimed at specific genetic mutations. However, many tumor-directed systemic therapies are ineffective in the brain.

In this review, we discuss the unique scientific and clinical challenges associated with treatment of brain tumors. We review existing roadblocks to drug delivery into the central nervous system (CNS), including the blood-brain barrier (BBB), blood-tumor barrier (BTB), and blood–cerebrospinal fluid (CSF) barrier (BCSFB), as well as therapeutic challenges posed by the CNS immune system and the immune suppressive microenvironment of brain tumors such as GBM. We also discuss the notion of tumor heterogeneity as a mechanism of treatment resistance and recent evidence challenging this paradigm in addition to the need for accurate noninvasive tumor markers for gliomas. In addition, we examine clinical challenges faced by neuro-oncologists in treating patients with brain tumor (including seizures, venous thromboembolism (VTE), neurologic dysfunction, and toxicities of treatment) as well as barriers to investigating new brain tumor therapies through clinical trials.

Key words
- Blood-brain barrier
- Blood-CSF barrier
- Brain tumors
- Glioblastoma
- Glioma
- Neuro-oncology
- Neurotoxicity

Abbreviations and Acronyms
AED: Antiepileptic drug
BBB: Blood-brain barrier
BCSFB: Blood–cerebrospinal fluid barrier
BTB: Blood-tumor barrier
CCNU: Lomustine
CNS: Central nervous system
CSF: Cerebrospinal fluid
GBM: Glioblastoma
IDH: Isocitrate dehydrogenase
KPS: Karnofsky Performance Status
MRS: Magnetic resonance spectroscopy
VTE: Venous thromboembolism
WBRT: Whole-brain radiotherapy

Weill Cornell Brain Tumor Center, Department of Neurology, Weill Cornell Medicine/New York-Presbyterian Hospital, New York, New York, USA

To whom correspondence should be addressed: Rajiv S. Magge, M.D. [E-mail: ram9116@med.cornell.edu]

Citation: World Neurosurg. (2021). https://doi.org/10.1016/j.wneu.2021.01.151

Journal homepage: www.journals.elsevier.com/world-neurosurgery

Available online: www.sciencedirect.com

FLA 5.6.0 DTD ■ WNEU16827_proof ■ 7 March 2021 ■ 12:45 am ■ ce

SCIENTIFIC CHALLENGES

Lack of Effective Drugs: Challenges Posed by the BBB, BTB, and BCSFB

The BBB is a cellular mechanism that acts as a protective interface between the peripheral blood and the CNS parenchyma, regulating the entry of substances such as toxins, ions, and macromolecules into the brain and spinal cord. The BBB is composed of neurovascular units comprising endothelial cells, pericytes, and astrocytic end feet.[2-4] Capillary beds in the brain parenchyma contain endothelial cells connected by tight junctions,[5] and these endothelial cells are surrounded by a basal lamina shared with pericytes and astrocytic end feet.[2,6] Tight junctions prevent toxins and other substances in the blood vessels from entering the brain parenchyma, whereas pericytes and astrocytic end feet regulate tight junctions and control transport of substances across the BBB.[7] Efflux pumps such as P-glycoprotein (ACBC1) and breast cancer—resistant protein (ABCG2) facilitate the transport of substances from the brain parenchyma into the blood, limiting CNS accumulation.[3,6]

The BBB plays a critical role in maintaining the homeostatic balance between the systemic circulation and the brain parenchyma and in protecting the CNS from harmful substances. However, the selective nature of the BBB poses a challenge with respect to drug delivery into the CNS, making treatment of certain neurologic conditions, including brain tumors, more difficult. To be effective in treating both primary and metastatic tumors of the CNS, drugs must penetrate the BBB and accumulate in tumor tissue in adequate concentrations. Small hydrophilic drugs and large molecules, including antibodies, are unable to penetrate the tight junctions created by endothelial cells, and lipophilic drugs that are able to cross lipid bilayers into the brain parenchyma may be ejected back into the blood by efflux pumps.[5]

Both primary and metastatic brain tumors disrupt the BBB, creating a unique BTB. The BTB is characterized by loss of astrocytic end feet and altered distribution of pericytes.[2,8] This disruption of the BBB could be considered beneficial, because it may permit drugs to penetrate the tumor; however, the BTB is associated with its own unique obstacles to drug delivery. The BTB and BBB in CNS tumors are both anatomically and physiologically heterogeneous. For example, a tumor core may have a disrupted BBB, whereas the tumor periphery maintains an intact one.[2] In GBM, essentially all tumors harbor both regions with a disrupted BBB and regions with an intact BBB.[5] Thus, the intact BBB continues to prevent drug delivery into those regions with functional efflux pumps and tight junctions. The BTB itself frequently retains efflux transporters despite disruption of the cellular mechanisms of the BBB. Further, although the BTB is more permeable than intact BBB and at times permits higher concentrations of drugs in regions with a disrupted BBB, this permeability is heterogeneous and does not permit uniform distribution of drugs into the tumor.[2]

In addition, the tumor microenvironment interacts with the BBB and plays a role in the support and growth of tumor cells as well as in hindering the effectiveness of tumor-directed therapies. Tumor progression leads to vascular dysfunction, and tumor cells are better able to tolerate the resultant hypoxic and acidic conditions than are normal cells. This hypoxic and acidic microenvironment contributes to chemoresistance and radioresistance in GBM and promotes an immunosuppressive microenvironment that also leads to treatment resistance.[2,9-11]

The BBB is responsible for regulating the homeostatic environment of the brain parenchyma. However, in the CSF spaces, this function is assumed by the BCSFB, which regulates the transport of substances between the systemic circulation and the CSF. This situation has significant implications in the pharmacologic treatment of leptomeningeal disease. The BCSFB is created by choroid plexus epithelial cells, which produce CSF, and their apical tight junctions, which inhibit paracellular diffusion of hydrophilic molecules.[12] Like the BBB, the BCSFB has mechanisms that allow transport of ions and nutrients from the blood into the CSF and removal of toxins from the CSF into the blood. However, the anatomy and physiology of the BCSFB differ from those of the BBB in a variety of ways.[12,13] Unlike the BBB, the BCSFB does contain some fenestrations. Various primary and metastatic neoplasms (including breast cancer, melanoma, and lymphoma) may spread to the leptomeninges/CSF spaces, which are diffuse given the circulation of CSF throughout the brain and spine. Thus, any chemotherapeutic or targeted agents intended to treat leptomeningeal disease must overcome the BCSFB (rather than the BBB) to penetrate and circulate through the CSF spaces in the entire neuroaxis.

The BBB, BTB, and BCSFB pose substantial challenges to drug delivery into the CNS. Overcoming these barriers has been a notable focus of research strategies designed to improve drug delivery to the CNS. Examples include focused ultrasonography to increase BBB permeability,[14,15] nanoparticles to improve CNS drug penetration,[16] and efflux pump inhibitors to prevent removal of drugs from the brain parenchyma.

Unique Anatomy and Physiology of the Immune System in the CNS

Cancer cells, including cells from primary brain tumors, have developed adaptive mechanisms that permit evasion from and interference with traditional immune responses. Immunotherapies, such as immune checkpoint inhibitors, stimulate the immune response and have revolutionized treatment in several systemic malignancies, including melanoma and certain subtypes of non-small-cell lung cancer. However, immunotherapies have thus far not been shown to have significant efficacy in the treatment of primary brain tumors such as glioma.

The unique anatomy and physiology of the immune system in the CNS pose a significant challenge to the use of immunotherapy in treating brain tumors. Historically, the CNS was considered an immunologically privileged site, with earlier studies indicating that heterotopic tissue grafts implanted in the CNS parenchyma did not elicit an immune response leading to graft rejection. However, the identification of the glial-lymphatic (glymphatic) system, a fluid and solute exchange system between the CSF and parenchymal interstitial fluid,[17,18] and the discovery of functioning meningeal lymphatic vessels[19,20] have fundamentally changed our perspectives regarding CNS immune privilege. The CNS is connected to both the afferent and efferent arms of the systemic immune system, but immunologic activity in the CNS is notably different in a few crucial ways.

Physical barriers, including the BBB and glia limitans, form compartments in the CNS that vary in their immune cell

accessibility and play key roles in the regulation of the immune system in the CNS.[21] The glia limitans is a barrier of astrocyte foot processes that surrounds the CNS parenchyma, and alongside the endothelial cell tight junctions of the BBB, helps regulate the passage of substances into the brain. Whereas the BBB regulates entry of immune cells into the CNS at postcapillary venules, the glia limitans prevents the access of adaptive immune cells into the brain parenchyma.[21,22] Interstitial fluids and solutes from the CNS parenchyma drain to lymph nodes along basement membranes in the walls of CNS capillaries and arteries without trafficking antigen-presenting cells.[21] The passage of immune cells into the CSF spaces is not as tightly regulated as in the brain parenchyma, and the BCSFB allows specific subsets of B and T cells to enter the CSF spaces, which then drain to deep cervical lymph nodes, allowing systemic passage of CD4+ T cells, monocytes, and dendritic cells.[21] The dural lymphatics that drain CSF into deep cervical lymph nodes are not directly connected to the CNS parenchyma. Thus, lymphatic drainage of interstitial fluid from the CSF, which includes trafficking of antigen-presenting cells, is distinct from drainage from the CNS parenchyma.[21] These physical barriers and tightly regulated immune functions (particularly in the CNS parenchyma) pose significant obstacles to the use of immunotherapies.

The CNS also contains unique immune cells contributing to different immune responses.[21,22] Microglia arising from yolk sac myeloid progenitor cells comprise the entirety of the population of resident myeloid cells in the CNS. Resident microglia are long-lived with low turnover rates and largely do not migrate to draining lymph nodes to present CNS antigens.[21] In the presence of an inflammatory stimulus, microglia undergo phenotypic changes, and additional macrophage populations are recruited from circulating monocytes[22]; environmental factors within the CNS affect the phenotype and activity of microglia and recruited macrophages.[22]

Immune Tumor Microenvironment

The tumor microenvironment includes tumor cells themselves as well as tumor stem cells, vascular endothelial cells, astrocytes, lymphocytes, extracellular matrix proteins, and cytokines.[11] The interaction between the tumor and its surroundings can produce an immunosuppressive microenvironment that fosters tumor growth and treatment resistance. Brain tumors such as gliomas have fewer tumor-infiltrating lymphocytes and other immune effector cells than many other malignancies.[22,23] As a result, they tend to have poor responses to immune checkpoint inhibitors despite the efficacy of these drugs in certain systemic malignancies. In addition, immune cells such as tumor-associated macrophages, myeloid-derived suppressor cells, T-regulatory cells, and natural killer cells are recruited by cancer stem cells and support chemoresistance, tumor invasiveness, and evasion of cancer cells from systemic immune surveillance.[10]

Despite the relatively low numbers of lymphocytes in the glioma microenvironment, tumor-associated macrophages promote tumor growth and constitute a substantial portion of the cellular microenvironment (up to 30% of tumor mass).[22,24,25] In addition, macrophages of bone marrow origin may migrate to and accumulate in the central areas of GBMs and exert immune suppression. Microglia and tumor-associated myeloid cells produce high levels of arginase, inhibiting T-cell proliferation and function by depleting surrounding arginine levels.[22,26] Like gliomas, brain metastases contain fewer T-cell infiltrates than do peripheral tumors and are associated with more microglia and macrophages, potentially inhibiting cell-mediated immune responses and contributing to the lack of response to immune checkpoint inhibitors in many cases.[22]

Tumor Heterogeneity

Classically, cancer therapies were designed to treat homogeneous diseases, with the presumption that tumors arise from a single cellular clone. However, recent evidence suggests that cancers, including primary brain tumors such as GBM, show genetic, epigenetic, developmental, and microenvironmental heterogeneity. Advanced genetic sequencing of tumor tissue has identified that GBM can show both intertumoral heterogeneity, with tumors at different anatomic locations showing different mutations, and intratumoral heterogeneity, with cells within the same tumor showing different and unique genetic alterations. Mutations in p53, estimated glomerular filtration rate, and platelet-derived growth factor α pathways differ among GBM cells within the same tumor.[27-29] Methylation of the O-6-methylguanine-DNA-methyltransferase promoter, which confers survival benefit and improved response to treatment in GBM,[1,30] can similarly vary among tumor cells.[31] Tumor cells can also evolve with time, acquiring mutations that may promote treatment resistance and disease progression. Therapies themselves may exert evolutionary pressure on tumor cells, causing treatment resistance. Certain Isocitrate dehydrogenase (*IDH*)-mutant low-grade astrocytomas treated with temozolomide recur as higher-grade, more malignant tumors that harbor a hypermutator phenotype, suggesting that temozolomide-induced hypermutation may drive malignant transformation in low-grade gliomas with subsequent poorer prognosis.[32]

Previously, GBM was characterized into at least 3 different transcriptomal expression-based subtypes (proneural, mesenchymal, and classic),with multiple subtypes coexisting in different parts of the same tumor.[33-35] The mesenchymal subtype was considered the most aggressive subtype and is associated with a poorer prognosis than the proneural subtype. It has been postulated that initial treatment with radiation therapy and chemotherapy promotes a proneural-mesenchymal transition in glioma stem cells, leading to a higher prevalence of mesenchymal glioma stem cells in the recurrent tumor and conferring a therapy-resistant phenotype.[34,36]

Recent advances in single-cell genomics have begun to question the true role of genomic heterogeneity in glioma therapeutic resistance, potentially creating a new paradigm. Single-cell data suggest that despite the many different genotypes found in *IDH*-wild-type gliomas, and despite the bulk RNA transcriptomic subtypes, all cells within a given GBM can be reduced down to 1 of 4 discrete cellular states, all of which are represented in all GBMs. Furthermore, the cellular states are plastic, allowing cellular transition from one state to another in what seems to be a stochastic manner.[37] If true, the therapeutic implications are that targeted therapy has not worked not because of intratumoral heterogeneity but rather because of failure to target a critical node in the oncogenic gene regulatory network. By contrast,

inhibition of core network master regulators could be effective against all such gliomas regardless of clonal genotype heterogeneity.[38]

Lack of Tumor Biomarkers

The heterogeneous nature of gliomas and their tendency to evolve over time create a substantial need for accurate and easily measured biomarkers that clarify disease status in real time. Molecular biomarkers associated with prognosis and treatment response, such as *IDH* mutation and 1/19q codeletion, or that could potentially serve as targets for treatment require surgical tissue sampling. Further, as noted earlier, gliomas genetically evolve over time, and recurrent tumors may have distinct genotypes, epigenetic features, and phenotypes from initial tumors. Thus, a single surgical sample captures the molecular status of the tumor at only a single time point and is not representative of the genetic profile of a tumor (and potential responsiveness to treatment) at recurrence. Neuroimaging (especially magnetic resonance imaging) is used to assess for disease progression; however, it can be limited in evaluating active, proliferating tumor, especially in cases of pseudoprogression after radiation therapy or immunotherapy.

Easily obtainable biomarkers that reflect the real-time tumor profile are necessary. Circulating serum and CSF biomarkers for gliomas are in development but have not been validated and are not yet usable in clinical practice.[39,40] The measurement of R(-)-2-hydroxyglutarate, a metabolite of mutant IDH activity, in magnetic resonance spectroscopy (MRS) has been developed as a potential imaging biomarker in *IDH*-mutant tumors.[41] Other imaging modalities, including proton MRS, thallium MRS, and functional diffusion mapping, are under investigation.[42] Development of biomarkers, whether through sampling of human fluids or through neuroimaging, that can reflect the evolving molecular landscape of CNS tumors and accurately detect tumor progression would be a tremendous advancement in neuro-oncology.

CLINICAL CHALLENGES

Neurologic and Medical Complications of CNS Tumors and Their Treatments

Brain tumors often lead to a variety of neurologic and medical issues, either as a direct consequence of the tumors themselves or as a result of tumor-directed therapies such as chemotherapy and radiation therapy. Neuro-oncologists must diagnose and manage the multiple neurologic and medical complications of CNS tumors and their treatments, including seizures, VTE, neurologic deficits, and toxicities of tumor-directed therapies, all of which can contribute to morbidity and greatly affect patients' quality of life.

Seizures. Seizures are a common complication of brain tumors and have a substantial impact on quality of life, including psychological well-being. Seizures are the presenting symptom in approximately 38% of patients with primary brain tumors and 20% of patients with brain metastases[43]; the overall frequency of seizures in GBM is approximately 59%.[44] GBM is the second most common cause of first-time seizures in older adults,[45] and seizures are the most common cause of emergency room presentations and hospitalizations in patients with GBM.[46,47] Patients with brain tumors who have had seizures often require treatment with antiepileptic drugs (AEDs), and decisions regarding starting and managing AED treatment are often made by the treating neuro-oncologist.

Seizures may occur in the perioperative setting, and multiple studies have been conducted examining the benefit of prophylactic AEDs in the perioperative period. Some studies have found that prophylactic AEDs such as levetiracetam reduce the risk of seizures during this period.[48] Others have found that the risk of toxicity of prophylactic AEDs such as phenytoin does not outweigh the potential benefit, as the incidence of postoperative seizures is low,[49] although many such studies were conducted with older drugs (e.g., phenytoin) with substantially more toxicity than newer agents, and their characterization of seizure incidence may have been inaccurate, because subclinical seizures are difficult to detect without continuous electroencephalogram monitoring. In patients with no previous history of seizures, prophylactic AEDs have not been shown to prevent first-time seizures.[50]

The American Academy of Neurology recommends against the routine use of prophylactic AEDs in patients with newly diagnosed brain tumors, because prophylactic AEDs have not been shown to be effective in preventing first-time seizures in this patient population.[51] Further, in patients with brain tumor who have not had a seizure, the American Academy of Neurology recommends tapering and discontinuing AEDs after the first postoperative week.[51] However, in practice, prophylactic AED use can be common despite these guidelines.[52] Patients who have had $\geq$1 seizures, either in the perioperative setting or otherwise, require treatment with AEDs to prevent further seizures, and decisions regarding discontinuing AEDs after a period of seizure freedom must be made on a case-by-case basis.

VTE. VTE (including both deep vein thrombosis and pulmonary embolism) is a common medical complication of brain tumors that contributes to morbidity and mortality. Malignancies are associated with hypercoagulability, likely related to disruption of the coagulation cascade, qualitative and quantitative platelet abnormalities, and tumor-directed therapies that promote hypercoagulability.[53-55] Patients with brain tumors are at particularly high risk for VTE given the hypercoagulable state associated with malignancies in general as well as additional risk factors such as limited mobility and the need for neurosurgical procedures. GBM carries a particularly high risk of VTE, and up to one third of patients with GBM develop VTE during the course of their illness.[56-58]

Patients with brain tumors who develop VTE require treatment with therapeutic anticoagulation, and neuro-oncologists must give consideration to the risk of intratumoral hemorrhage when making decisions regarding initiation of this treatment. Risk of intracranial hemorrhage in patients with malignant gliomas on anticoagulation therapy has not been shown to be significantly higher than in patients who are not receiving this treatment.[59] However, certain brain metastases, such as metastases from melanoma, have a propensity to hemorrhage, and hemorrhagic metastases may complicate use of therapeutic anticoagulation. Patients with brain tumors who develop VTE should be treated

with therapeutic anticoagulation unless they have active intracranial hemorrhage or hemorrhagic tumors, coagulopathy, or significant thrombocytopenia.[60] With respect to prophylactic anticoagulation, a combination of chemical VTE prophylaxis with low-molecular-weight heparin and mechanical VTE prophylaxis has been shown to reduce risk of VTE in patients with brain tumor undergoing craniotomy.[61] A randomized trial examining the use of prophylactic anticoagulation in patients with newly diagnosed malignant gliomas failed to show a benefit in reducing VTE,[62] and prophylactic anticoagulation is not recommended outside the perioperative setting.

Neurologic Deficits and Functional Impairment. Brain tumors are associated with substantial neurologic deficits as a direct result of injury to the brain by the tumors themselves and/or as a consequence of surgery on the tumor. Focal neurologic deficits such as motor weakness (and associated impairment in gait and mobility), sensory impairment (including hemisensory neglect), aphasia, apraxia, dysarthria, and dysphagia are common neurologic complications of brain tumors that can lead to significant morbidity and adversely affect quality of life. Even benign or low-grade tumors otherwise responsive to treatment can cause debilitating neurologic deficits depending on their anatomic location. Poor performance status, often measured by the Karnofsky Performance Status (KPS), is associated with worse prognosis and poor tolerance of treatment in patients with brain tumors; in patients with high-grade gliomas, performance status is independently associated with prognosis, and worse performance status is associated with worse prognosis.[63,64] As a result of the neurologic impairment caused by brain tumors, rehabilitation programs (including physical therapy, occupational therapy, and speech therapy) are indispensable tools in the care of patients with brain tumor. Patients with brain tumors treated in acute rehabilitation settings after tumor resection have shown improvement in neurologic deficits similar to those experienced by patients with other neurologic conditions such as strokes and traumatic brain injury.[65,66] Outpatient rehabilitation programs, including cognitive therapy, have also shown benefit in patients with brain tumor.[65]

Toxicities of Tumor-Directed Therapies. *Systemic Therapies.* Although brain tumors themselves are associated with a variety of neurologic and medical complications, tumor-directed therapies such as chemotherapy, targeted therapies, immunotherapy, antiangiogenic therapy, and radiation therapy also have medical consequences. Temozolomide, which is commonly used in the treatment of both high-grade and low-grade gliomas, is associated with nausea, anorexia, and constipation as well as bone marrow suppression and, more rarely, hepatotoxicity.[67] The combination of lomustine (CCNU), procarbazine, and vincristine (i.e., PCV) is frequently used in the treatment of oligodendrogliomas. Common side effects of CCNU include nausea and bone marrow suppression with resultant leukopenia and thrombocytopenia. Rarely, treatment with CCNU can lead to pulmonary toxicity, including interstitial pneumonia and pulmonary fibrosis, and routine monitoring of pulmonary function tests is required in patients treated with this drug. Procarbazine is associated with bone marrow suppression, nausea, vomiting, acute encephalopathy, and cerebellar toxicity.[68] In addition, procarbazine is a monoamine oxidase inhibitor, and, in combination with tyramine-containing foods, can precipitate a hypertensive crisis; procarbazine can also lead to serotonin syndrome when used in combination with other serotonergic agents. Potential side effects of vincristine include peripheral neuropathy, cerebellar dysfunction, acute encephalopathy, and constipation, which can lead to paralytic ileus.[68] Vincristine is also associated with hepatic sinusoidal obstruction syndrome.

Bevacizumab, a vascular endothelial growth factor inhibitor, is frequently used in the treatment of recurrent GBM, particularly in patients with symptomatic peritumoral edema. However, bevacizumab is associated with several, potentially severe side effects, including hypertension, proteinuria, bowel perforation, impaired wound healing, and increased risk for both thromboembolism (including deep vein thrombosis, pulmonary embolism, myocardial infarction, and stroke) and hemorrhage (including intracranial hemorrhage). High-dose intravenous methotrexate, which is the backbone of medical treatment for primary CNS lymphoma, may cause renal toxicity (including acute renal failure), bone marrow suppression, hepatotoxicity, and diarrhea. Additional neurologic toxicities with high-dose methotrexate include acute encephalopathy, chronic leukoencephalopathy, aseptic meningitis, and seizures.[68] All these medical and neurologic toxicities may limit cancer treatment in affected patients. Neuro-oncologists must manage these adverse effects when they occur and weigh the benefit of initiating or continuing any given treatment against the risk of toxicity.

Radiation Therapy. Radiation therapy, a mainstay of treatment in both primary and metastatic CNS tumors, is associated with its own unique set of toxicities. Whole-brain radiotherapy (WBRT) is primarily used in the treatment of patients with a large burden of brain metastases and, at times, for recurrent primary CNS lymphoma. Involved-field radiation, which is localized to the region of the tumor and a small margin of tissue surrounding the tumor, is often used in the treatment of gliomas and reduces the dose and volume of radiation to normal surrounding brain tissue. Stereotactic radiosurgery uses convergent beams to deliver a large dose of radiation to a small area and is used in the treatment of patients with a limited number of brain metastases and in well-circumscribed lesions such as meningiomas.

All 3 of these modalities can increase edema associated with brain tumors, leading to focal neurologic deficits and, potentially, signs and symptoms of increased intracranial pressure.[69] Additional short-term complications of radiation therapy include fatigue, alopecia, and dermatitis. Radiation therapy may also lead to radiation necrosis, which can occur months to years after completion of radiation, contributing to focal neurologic deficits as well as symptoms attributable to increased intracranial pressure such as headaches. Neuro-oncologists often treat neurologic symptoms caused by radiation necrosis with corticosteroids and must manage their initiation and dosing schedule. In addition, radiation necrosis is characterized by enhancement with gadolinium contrast on magnetic resonance imaging and can be mistaken for tumor progression. Radiation therapy, namely involved-field radiation therapy and WBRT, is also associated with late-onset neurotoxicity, with cerebral atrophy and resultant neurologic symptoms such as cognitive impairment, incontinence,

mood and personality changes, and gait ataxia, which may occur years to decades after treatment.[69] Certain chemotherapies (including intravenous and intrathecal methotrexate, vincristine, and high-dose cytarabine) can potentiate the neurotoxic effects of radiation therapy.[69] Long-term neurologic consequences of radiation therapy may cause significant debility and adversely affect quality of life. Limiting radiation treatment fields, total dose, and fractional size in the treatment of brain tumors as well as using a hippocampal-sparing strategy with WBRT can all reduce the likelihood of neurocognitive sequelae from radiation.[70,71] In addition, a randomized trial suggested that the addition of memantine decreased some of the neurologic sequelae of WBRT.[72]

Clinical Trials

The prognosis for many CNS tumors, particularly high-grade gliomas such as GBM, remains poor despite treatment with surgery, radiation therapy, and chemotherapy. Thus, clinical trials investigating new drug therapies are critical in establishing new treatment paradigms for these largely fatal tumors. Some studies have found that clinical trial participation is associated with a survival benefit in patients with GBM.[73] However, only approximately 28% of neuro-oncology patients are referred for clinical trials,[74] and as few as 8%–11% of patients with newly diagnosed GBM may enroll in clinical trials.[75] Several roadblocks exist in testing new drug therapies for CNS tumors, particularly with respect to enrolling patients in clinical trials.

There is a suboptimal pipeline of drugs available for testing in clinical trials. As described in the section on "Scientific Challenges," gliomas and other brain tumors are unique in their mechanisms of resistance to drug therapies, with the BBB, BTB, and BCSFB preventing drug delivery into the CNS and the CNS immune system and tumor microenvironment limiting efficacy of immunotherapies. In addition, preclinical models for CNS tumors such as GBM are not always representative of the in vivo tumor microenvironment and behavior. Thus, drugs that are effective for systemic malignancies may not necessarily be equally effective in treating CNS tumors. Moreover, drugs that seem effective in preclinical tumor models may not be equally effective when tested in patients. In addition, long development times for drugs affect the pipeline of medications available for testing in clinical trials. For drugs that complete phase 1 testing, development time from phase 2 to the end of phase 3 can be 7.2 years on average,[75] further delaying the availability of potential treatments.

In addition to the lack of potentially efficacious drugs used in clinical trials, lack of pharmaceutical company support also poses a challenge to the success of clinical trials for patients with brain tumors. Compared with systemic malignancies such as lung cancer and breast cancer, primary brain tumors such as gliomas are relatively rare.[76] Approximately 51% of clinical trials for GBM are funded by industry, and industrial funding is largely focused on systemic therapies rather than surgical or radiation techniques.[77] Given the relative rarity of primary brain tumors compared with systemic malignancies, there may not be so much commercial incentive to investigate novel treatments for brain tumors, particularly nondrug interventions.

Furthermore, clinical trials are highly resource intensive, and lack of appropriate resources for conducting them limits the number of locations at which clinical trials are available to patients. Patients participating in clinical trials often require frequent office visits and monitoring, including close monitoring of laboratory tests and potential adverse effects of the treatment being studied. Dedicated experimental clinical and research teams are necessary to conduct patient care and perform all necessary monitoring required by the trial. The principal investigator helps to develop the concept for the trial and write the trial protocol; in addition, they must submit protocols for institutional review board approval, direct the recruitment of patients, and supervise data collection, analysis, and interpretation.[78] Staff clinicians and nurses are needed to treat patients according to the trial protocol and manage patient care. In addition, dedicated research nurses are needed to manage data collection, assist in the informed consent process, educate patients and staff about clinical trials, and conduct assessments for adverse events.[78] Clinical trials also necessitate the use of data managers to manage data collection and tracking, provide data to monitoring agencies, and prepare summaries for interim and final data analyses.[78] Academic institutions will have protocol review and monitoring committees composed of investigators from various disciplines to review the scientific merit of cancer research protocols and monitor their progress. Given the large number of personnel required to conduct clinical trials and the specialized training that they must receive for their roles, many centers are not equipped for clinical trials, limiting their availability to large academic (and often urban) medical centers. Lack of availability of clinical trials close to patients' homes is a substantial barrier to study accrual, especially because patients in clinical trials are required to adhere to strict follow-up schedules with more frequent follow-up and monitoring than patients who are not participating in such studies.[74] Increased travel distance to the site of the clinical trial has been associated with lack of participation in clinical trials in patients with GBM.[79]

Clinical trials of brain tumor treatments are often slow to accrue patients for a variety of additional reasons. Many clinical trials for gliomas investigate treatments for recurrent disease. However, patients often have poorer performance status at the time of disease recurrence, which may preclude them from participation in clinical trials, because trials often require patients to have a KPS above a certain value, indicating reasonably good performance status. Further, elderly patients and patients with poor KPS with both primary brain tumors and systemic malignancies have greater degrees of toxicity with tumor-directed therapies.[80,81] The incidence of GBM increases with age, and because many patients with GBM have neurologic deficits that affect their performance status, such patients are often not eligible for participation in clinical trials. Patients with altered mental status, in particular, have been shown to have lower enrollment in clinical trials compared with patients with other signs and symptoms.[79] Moreover, college-educated patients and patients with active employment are more likely to enroll in clinical trials for GBM than are patients with less formal education and without active employment, suggesting that lower levels of education and socioeconomic stability are barriers to trial enrollment.[79] In addition, trials may be slow to accrue patients because of providers' hesitance to refer patients for experimental therapies. Potential barriers to provider referral to trials include geography,

FLA 5.6.0 DTD ■ WNEU16827_proof ■ 7 March 2021 ■ 12:45 am ■ ce

belief that patients may not be able to travel to the study site regularly, and perception that patients may not qualify for any clinical trials.[74]

CONCLUSIONS

Treatment of brain tumors, particularly malignant primary brain tumors such as GBM, is associated with a unique set of scientific and clinical challenges. With respect to scientific challenges, the BBB, BTB, and BCSFB prevent adequate drug delivery into the brain parenchyma and CSF spaces. In addition, the anatomy and physiology of the immune system in the CNS complicate the use of immunotherapies in treating gliomas, and the immunosuppressive microenvironment contributes to tumor protection and treatment resistance, including the ineffectiveness of immunotherapies.

Further, both intratumoral and intertumoral heterogeneity may contribute to multitherapy resistance in gliomas, although this paradigm has been challenged by recent evidence. Easily obtainable biomarkers that reflect the molecular characteristics of tumors and disease status in real time are needed.

Neuro-oncologists also face a variety of clinical challenges in treating patients with brain tumor. Patients with brain tumors frequently experience neurologic deficits as a result of their tumors, and the medical and neurologic consequences of brain tumors and their treatments contribute to morbidity and mortality from brain tumors and complicate treatment. There is a crucial need for new treatment paradigms to be investigated through clinical trials, but there are several roadblocks to availability of clinical trials and to patient enrollment. Efforts made to address these specific challenges in brain tumor treatment may serve to improve treatment response and prognosis in these devastating diseases.

ACKNOWLEDGMENTS

We acknowledge the contribution of Anne Stanford, E.L.S., who Q3 provided professional editing services.

REFERENCES

1. Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med*. 2005;352:987-996.
2. Arvanitis CD, Ferraro GB, Jain RK. The blood-brain barrier and blood-tumour barrier in brain tumours and metastases. *Nat Rev Cancer*. 2020;20:26-41.
3. Banks WA. From blood-brain barrier to blood-brain interface: new opportunities for CNS drug delivery. *Nat Rev Drug Discov*. 2016;15:275-292.
4. Abbott NJ. Blood-brain barrier structure and function and the challenges for CNS drug delivery. *J Inherit Metab Dis*. 2013;36:437-449.
5. Oberoi RK, Parrish KE, Sio TT, Mittapalli RK, Elmquist WF, Sarkaria JN. Strategies to improve delivery of anticancer drugs across the blood-brain barrier to treat glioblastoma. *Neuro Oncol*. 2016;18:27-36.
6. Berghoff AS, Preusser M. Role of the blood-brain barrier in metastatic disease of the central nervous system. *Handb Clin Neurol*. 2018;149:57-66.
7. Sweeney MD, Ayyadurai S, Zlokovic BV. Pericytes of the neurovascular unit: key functions and signaling pathways. *Nat Neurosci*. 2016;19:771-783.
8. Dubois LG, Campanati L, Righy C, et al. Gliomas and the vascular fragility of the blood brain barrier. *Front Cell Neurosci*. 2014;8:418.
9. Quail DF, Joyce JA. The microenvironmental landscape of brain tumors. *Cancer Cell*. 2017;31:326-341.
10. Da Ros M, De Gregorio V, Iorio AL, et al. Glioblastoma chemoresistance: the double play by microenvironment and blood-brain barrier. *Int J Mol Sci*. 2018;19:2879.
11. Jackson C, Ruzevick J, Phallen J, Belcaid Z, Lim M. Challenges in immunotherapy presented by the glioblastoma multiforme microenvironment. *Clin Dev Immunol*. 2011;2011:732413.
12. Engelhardt B, Sorokin L. The blood-brain and the blood-cerebrospinal fluid barriers: function and dysfunction. *Semin Immunopathol*. 2009;31:497-511.
13. Tumani H, Huss A, Bachhuber F. The cerebrospinal fluid and barriers—anatomic and physiologic considerations. *Handb Clin Neurol*. 2017;146:21-32.
14. Aryal M, Arvanitis CD, Alexander PM, McDannold N. Ultrasound-mediated blood-brain barrier disruption for targeted drug delivery in the central nervous system. *Adv Drug Deliv Rev*. 2014;72:94-109.
15. Arvanitis CD, Askoxylakis V, Guo Y, et al. Mechanisms of enhanced drug delivery in brain metastases with focused ultrasound-induced blood-tumor barrier disruption. *Proc Natl Acad Sci U S A*. 2018;115:E8717-E8726.
16. Angeli E, Nguyen TT, Janin A, Bousquet G. How to make anticancer drugs cross the blood-brain barrier to treat brain metastases. *Int J Mol Sci*. 2019;21:22.
17. Iliff JJ, Wang M, Liao Y, et al. A paravascular pathway facilitates CSF flow through the brain parenchyma and the clearance of interstitial solutes, including amyloid β. *Sci Transl Med*. 2012;4:147ra111.
18. Kipnis J. Multifaceted interactions between adaptive immunity and the central nervous system. *Science*. 2016;353:766-771.
19. Aspelund A, Antila S, Proulx ST, et al. A dural lymphatic vascular system that drains brain interstitial fluid and macromolecules. *J Exp Med*. 2015;212:991-999.
20. Louveau A, Herz J, Alme MN, et al. CNS lymphatic drainage and neuroinflammation are regulated by meningeal lymphatic vasculature. *Nat Neurosci*. 2018;21:1380-1391.
21. Engelhardt B, Vajkoczy P, Weller RO. The movers and shapers in immune privilege of the CNS. *Nat Immunol*. 2017;18:123-131.
22. Sampson JH, Gunn MD, Fecci PE, Ashley DM. Brain immunology and immunotherapy in brain tumours. *Nat Rev Cancer*. 2020;20:12-25.
23. Gajewski TF, Schreiber H, Fu YX. Innate and adaptive immune cells in the tumor microenvironment. *Nat Immunol*. 2013;14:1014-1022.
24. Graeber MB, Scheithauer BW, Kreutzberg GW. Microglia in brain tumors. *Glia*. 2002;40:252-259.
25. Hambardzumyan D, Gutmann DH, Kettenmann H. The role of microglia and macrophages in glioma maintenance and progression. *Nat Neurosci*. 2016;19:20-27.
26. Zhang I, Alizadeh D, Liang J, et al. Characterization of arginase expression in glioma-associated microglia and macrophages. *PLoS One*. 2016;11:e0165118.
27. Noch EK, Ramakrishna R, Magge R. Challenges in the treatment of glioblastoma: multisystem mechanisms of therapeutic resistance. *World Neurosurg*. 2018;116:505-517.
28. Szerlip NJ, Pedraza A, Chakravarty D, et al. Intratumoral heterogeneity of receptor tyrosine kinases EGFR and PDGFRA amplification in glioblastoma defines subpopulations with distinct growth factor response. *Proc Natl Acad Sci U S A*. 2012;109:3041-3046.
29. Kumar A, Boyle EA, Tokita M, et al. Deep sequencing of multiple regions of glial tumors reveals spatial heterogeneity for mutations in clinically relevant genes. *Genome Biol*. 2014;15:530.

30. Hegi ME, Diserens AC, Gorlia T, et al. MGMT gene silencing and benefit from temozolomide in glioblastoma. *N Engl J Med*. 2005;352:997-1003.

31. Parker NR, Hudson AL, Khong P, et al. Intratumoral heterogeneity identified at the epigenetic, genetic and transcriptional level in glioblastoma. *Sci Rep*. 2016;6:22477.

32. Johnson BE, Mazor T, Hong C, et al. Mutational analysis reveals the origin and therapy-driven evolution of recurrent glioma. *Science*. 2014;343:189-193.

33. Patel AP, Tirosh I, Trombetta JJ, et al. Single-cell RNA-seq highlights intratumoral heterogeneity in primary glioblastoma. *Science*. 2014;344:1396-1401.

34. Fedele M, Cerchia L, Pegoraro S, Sgarra R, Manfioletti G. Proneural-mesenchymal transition: phenotypic plasticity to acquire multitherapy resistance in glioblastoma. *Int J Mol Sci*. 2019;20:2746.

35. Verhaak RG, Hoadley KA, Purdom E, et al. Integrated genomic analysis identifies clinically relevant subtypes of glioblastoma characterized by abnormalities in PDGFRA, IDH1, EGFR, and NF1. *Cancer Cell*. 2010;17:98-110.

36. Segerman A, Niklasson M, Haglund C, et al. Clonal variation in drug and radiation response among glioma-initiating cells is linked to proneural-mesenchymal transition. *Cell Rep*. 2016;17:2994-3009.

37. Neftel C, Laffy J, Filbin MG, et al. An integrative model of cellular states, plasticity, and genetics for glioblastoma. *Cell*. 2019;178:835-849.e821.

38. Pine AR, Cirigliano SM, Nicholson JG, et al. Tumor microenvironment is critical for the maintenance of cellular states found in primary glioblastomas. *Cancer Discov*. 2020;10:964-979.

39. Westphal M, Lamszus K. Circulating biomarkers for gliomas. *Nat Rev Neurol*. 2015;11:556-566.

40. Mattox AK, Yan H, Bettegowda C. The potential of cerebrospinal fluid-based liquid biopsy approaches in CNS tumors. *Neuro Oncol*. 2019;21:1509-1518.

41. Pope WB, Prins RM, Albert Thomas M, et al. Non-invasive detection of 2-hydroxyglutarate and other metabolites in IDH1 mutant glioma patients using magnetic resonance spectroscopy. *J Neurooncol*. 2012;107:197-205.

42. Nicolaidis S. Biomarkers of glioblastoma multiforme. *Metabolism*. 2015;64(3 suppl 1):S22-S27.

43. Lynam LM, Lyons MK, Drazkowski JF, et al. Frequency of seizures in patients with newly diagnosed brain tumors: a retrospective review. *Clin Neurol Neurosurg*. 2007;109:634-638.

44. Vecht C, Royer-Perron L, Houillier C, Huberfeld G. Seizures and anticonvulsants in brain tumours: frequency, mechanisms and antiepileptic management. *Curr Pharm Des*. 2017;23:6464-6487.

45. Sander JW, Hart YM, Johnson AL, Shorvon SD. National General practice study of epilepsy: newly diagnosed epileptic seizures in a general population. *Lancet*. 1990;336:1267-1271.

46. Mohile NA. Medical complications of brain tumors. *Continuum (Minneap Minn)*. 2017;23(6 Neuro-oncology):1635-1652.

47. Wasilewski A, Serventi J, Kamalyan L, Wychowski T, Mohile N. Acute care in glioblastoma: the burden and the consequences. *Neuro-oncol Pract*. 2017;4:248-254.

48. Iuchi T, Kuwabara K, Matsumoto M, Kawasaki K, Hasegawa Y, Sakaida T. Levetiracetam versus phenytoin for seizure prophylaxis during and early after craniotomy for brain tumours: a phase II prospective, randomised study. *J Neurol Neurosurg Psychiatry*. 2015;86:1158-1162.

49. Wu AS, Trinh VT, Suki D, et al. A prospective randomized trial of perioperative seizure prophylaxis in patients with intraparenchymal brain tumors. *J Neurosurg*. 2013;118:873-883.

50. Tremont-Lukats IW, Ratilal BO, Armstrong T, Gilbert MR. Antiepileptic drugs for preventing seizures in people with brain tumors. *Cochrane Database Syst Rev*. 2008:CD004424.

51. Glantz MJ, Cole BF, Forsyth PA, et al. Practice parameter: anticonvulsant prophylaxis in patients with newly diagnosed brain tumors. Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*. 2000;54:1886-1893.

52. Lapointe S, Florescu M, Nguyen DK, Djeffal C, Belanger K. Prophylactic anticonvulsants for gliomas: a seven-year retrospective analysis. *Neuro-oncol Pract*. 2015;2:192-198.

53. Levitan N, Dowlati A, Remick SC, et al. Rates of initial and recurrent thromboembolic disease among patients with malignancy versus those without malignancy. Risk analysis using Medicare claims data. *Medicine (Baltimore)*. 1999;78:285-291.

54. Sack GH Jr, Levin J, Bell WR. Trousseau's syndrome and other manifestations of chronic disseminated coagulopathy in patients with neoplasms: clinical, pathophysiologic, and therapeutic features. *Medicine (Baltimore)*. 1977;56:1-37.

55. Rickles FR, Levine M, Edwards RL. Hemostatic alterations in cancer patients. *Cancer Metastasis Rev*. 1992;11:237-248.

56. Brandes AA, Scelzi E, Salmistraro G, et al. Incidence of risk of thromboembolism during treatment high-grade gliomas: a prospective study. *Eur J Cancer*. 1997;33:1592-1596.

57. Marras LC, Geerts WH, Perry JR. The risk of venous thromboembolism is increased throughout the course of malignant glioma: an evidence-based review. *Cancer*. 2000;89:640-646.

58. Edwin NC, Khoury MN, Sohal D, McCrae KR, Ahluwalia MS, Khorana AA. Recurrent venous thromboembolism in glioblastoma. *Thromb Res*. 2016;137:184-188.

59. Ruff RL, Posner JB. Incidence and treatment of peripheral venous thrombosis in patients with glioma. *Ann Neurol*. 1983;13:334-336.

60. Lyman GH, Khorana AA, Kuderer NM, et al. Venous thromboembolism prophylaxis and treatment in patients with cancer: American Society of Clinical Oncology clinical practice guideline update. *J Clin Oncol*. 2013;31:2189-2204.

61. Alshehri N, Cote DJ, Hulou MM, et al. Venous thromboembolism prophylaxis in brain tumor patients undergoing craniotomy: a meta-analysis. *J Neurooncol*. 2016;130:561-570.

62. Perry JR, Julian JA, Laperriere NJ, et al. PRODIGE: a randomized placebo-controlled trial of dalteparin low-molecular-weight heparin thromboprophylaxis in patients with newly diagnosed malignant glioma. *J Thromb Haemost*. 2010;8:1959-1965.

63. Lacroix M, Abi-Said D, Fourney DR, et al. A multivariate analysis of 416 patients with glioblastoma multiforme: prognosis, extent of resection, and survival. *J Neurosurg*. 2001;95:190-198.

64. Bauchet L, Mathieu-Daude H, Fabbro-Peray P, et al. Oncological patterns of care and outcome for 952 patients with newly diagnosed glioblastoma in 2004. *Neuro Oncol*. 2010;12:725-735.

65. Vargo M, Henriksson R, Salander P. Rehabilitation of patients with glioma. *Handb Clin Neurol*. 2016;134:287-304.

66. Vargo M. Brain tumor rehabilitation. *Am J Phys Med Rehabil*. 2011;90(5 suppl 1):S50-S62.

67. Bae SH, Park MJ, Lee MM, et al. Toxicity profile of temozolomide in the treatment of 300 malignant glioma patients in Korea. *J Korean Med Sci*. 2014;29:980-984.

68. DeAngelis LM, Posner JB. Side effects of chemotherapy. In: Gilman S, Herdman WJ, eds. *Neurologic Complications of Cancer*. 2nd ed. Oxford: Oxford University Press; 2009:447-510.

69. DeAngelis LM, Posner JB. Side effects of radiation therapy. In: Gilman S, Herdman WJ, eds. *Neurologic Complications of Cancer*. 2nd ed. Oxford: Oxford University Press; 2009:511-555.

70. Laack NN, Brown PD. Cognitive sequelae of brain radiation in adults. *Semin Oncol*. 2004;31:702-713.

71. Brown PD, Gondi V, Pugh S, et al. Hippocampal avoidance during whole-brain radiotherapy plus memantine for patients with brain metastases: phase III trial NRG Oncology CC001. *J Clin Oncol*. 2020;38:1019-1029.

72. Brown PD, Pugh S, Laack NN, et al. Memantine for the prevention of cognitive dysfunction in patients receiving whole-brain radiotherapy: a randomized, double-blind, placebo-controlled trial. *Neuro Oncol*. 2013;15:1429-1437.

73. Field KM, Drummond KJ, Yilmaz M, et al. Clinical trial participation and outcome for patients with glioblastoma: multivariate analysis from a comprehensive dataset. *J Clin Neurosci*. 2013;20:783-789.

74. Rogers JL, Acquaye A, Vera E, Bates A, Wen PY, Armstrong TS. Provider-reported challenges and barriers to referring patients to neuro-oncology clinical trials: a report from the Society for

Neuro-Oncology member survey. *Neurooncol Pract*. 2020;7:38-51.

75. Vanderbeek AM, Rahman R, Fell G, et al. The clinical trials landscape for glioblastoma: is it adequate to develop new treatments? *Neuro Oncol*. 2018;20:1034-1043.

76. Ostrom QT, Gittleman H, Fulop J, et al. CBTRUS statistical report: primary brain and central nervous system tumors diagnosed in the United States in 2008-2012. *Neuro Oncol*. 2015;17(suppl 4): iv1-iv62.

77. Cihoric N, Tsikkinis A, Minniti G, et al. Current status and perspectives of interventional clinical trials for glioblastoma—analysis of ClinicalTrials.gov. *Radiat Oncol*. 2017;12:1.

78. National Cancer Institute. Research team members. Available at: https://www.cancer.gov/about-cancer/treatment/clinical-trials/what-are-trials/team. Accessed April 25, 2020.

79. Harrison RA, Anderson MD, Cachia D, et al. Clinical trial participation of patients with glioblastoma at The University of Texas MD Anderson Cancer Center. *Eur J Cancer*. 2019;112:83-93.

80. Sargent DJ, Kohne CH, Sanoff HK, et al. Pooled safety and efficacy analysis examining the effect of performance status on outcomes in nine first-line treatment trials using individual data from patients with metastatic colorectal cancer. *J Clin Oncol*. 2009;27:1948-1955.

81. Sijben AE, McIntyre JB, Roldan GB, et al. Toxicity from chemoradiotherapy in older patients with glioblastoma multiforme. *J Neurooncol*. 2008;89: 97-103.

Conflict of interest statement: The authors declare that the article content was composed in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received 27 January 2021; accepted 28 January 2021

Citation: World Neurosurg. (2021). https://doi.org/10.1016/j.wneu.2021.01.151

*Journal homepage: **www.journals.elsevier.com/world-neurosurgery***

*Available online: **www.sciencedirect.com***