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Medical management of brain tumors and the sequelae of treatment

David Schiff†, Eudocia Q. Lee, Lakshmi Nayak, Andrew D. Norden, David A. Reardon, and Patrick Y. Wen

Neuro-Oncology Center, University of Virginia Medical Center, Charlottesville, Virginia (D.S.); Center for Neuro-Oncology, Dana-Farber Cancer Institute and Harvard Medical School, Boston, Massachusetts (E.Q.L., L.N., A.D.N., D.A.R., P.Y.W.)

Corresponding Author: David Schiff, MD, Neuro-Oncology Center, Hospital West, Room 6225, Jefferson Park Avenue, Charlottesville, VA 22908-0432 (ds4jd@virginia.edu).

†All authors contributed equally to this manuscript.

Patients with malignant brain tumors are prone to complications that negatively impact their quality of life and sometimes their overall survival as well. Tumors may directly provoke seizures, hypercoagulable states with resultant venous thromboembolism, and mood and cognitive disorders. Antitumor treatments and supportive therapies also produce side effects. In this review, we discuss major aspects of supportive care for patients with malignant brain tumors, with particular attention to management of seizures, venous thromboembolism, corticosteroids and their complications, chemotherapy including bevacizumab, and fatigue, mood, and cognitive dysfunction.

Keywords: bevacizumab, brain tumor, chemotherapy, cognition, complications, corticosteroids, fatigue, mood, seizure, symptom management, vasogenic edema, venous thromboembolism.

While occasional patients with brain tumors undergo curative therapy and are left without sequelae, most patients with malignant tumors face a chronic condition that predisposes them to seizures, hypercoagulability, and mood and cognitive disorders. Antineoplastic therapies and corticosteroids may exacerbate mood disorders and cause cytopenia and infections. A substantial part of neuro-oncology clinical practice is necessarily devoted to supportive care management. Herein, we review the literature on the medical management of issues commonly confronting brain tumor patients. This manuscript focuses on the most common and important side effects and treatment complications encountered in the care of adult brain tumor patients.

Seizures in Brain Tumor Patients

Seizures are among the most frequent clinical manifestations of brain tumors. An overall estimate of seizure risk in brain tumor patients is misleading because the figure varies widely as a function of tumor histology, location, and growth rate. At one end of the spectrum are gangliogliomas and dysembryoplastic neuroepithelial tumors, which are associated with intractable epilepsy in at least 90% of patients.[1] Surgical resection is often a highly effective treatment for these lesions, both in terms of recurrence-free survival[2] and seizure control.[3] Diffuse low-grade gliomas also provoke seizures in more than 80% of patients, often as the presenting symptom.[4] In this cohort, seizures may be more common in patients with oligodendroglial tumors, which tend to involve the cortex,[5] and in lesions of the temporal lobe and insula.[6] In both adult and pediatric low-grade gliomas, gross total resection is a strong predictor of postoperative seizure freedom.[4,7] Seizures are the presenting symptom in only ~20% of patients with supratentorial high-grade gliomas, perhaps because of their rapid growth. Seizures occur at some stage of the illness in 30%–50% of high-grade glioma patients.[8,9] Tumors isolated to white matter and the posterior fossa do not often cause seizures, although deep tumors are frequently multifocal and thus are potentially epileptogenic. Brain metastases cause seizures in 20%–40% of patients, particularly when they are hemorrhagic, multifocal, or involve the temporal lobe.[10]

Retrospective data suggest that antitumor therapy may have a favorable impact on seizure control in brain tumor patients.[11] In one study, 39 low-grade glioma patients treated with temozolomide had a higher rate of reduction in seizure frequency compared with a matched cohort that was not treated with temozolomide (59% vs 13%, $P < .001$).[12] This observation was independent of changes in the antiepileptic drug (AED) regimen. Other reports suggested a similar therapeutic benefit for patients treated with radiation therapy.[13,14] However, a retrospective series of 1509 patients with low-grade gliomas showed no significant improvement in seizure control for patients treated with chemotherapy or radiation therapy.[4] This issue will remain controversial until it is addressed definitively in prospective fashion.

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Use of Antiepileptic Drugs

The standard of care for brain tumor patients who present with seizures includes the administration of AEDs.[15] Conversely, there is no consensus in daily clinical practice regarding the administration of prophylactic AEDs to patients with supratentorial tumors who have not had seizures. In a 1996 survey of practice patterns, 33% of radiation oncologists, 50% of oncologists, 53% of neurologists, and 81% of neurosurgeons reported administering prophylactic AEDs. The overall rate of prophylactic AED administration was 55%.[16] A retrospective study showed that 27% of 164 brain tumor patients treated in Canada between 2003 and 2005 received phenytoin despite a negative history of seizures.[17]

Several studies have evaluated the usefulness of AED therapy for brain tumor patients with no history of seizures and have produced conflicting results (Table 1). Most of these have included patients with gliomas, brain metastases, and meningiomas, in varying proportions. Many brain tumor patients are treated with AEDs because they have had a craniotomy. It is unclear, however, whether prolonged prophylactic AED therapy reduces the frequency of seizures after craniotomy. In a prospective trial involving 276 consecutive supratentorial craniotomy patients (including 50 with meningiomas) who were randomized postoperatively to receive an AED or no treatment, there was no difference in the incidence of seizures (37%) or death between the 2 groups, suggesting that prophylactic AED therapy may not be routinely necessary after craniotomy.[18] A meta-analysis of 6 controlled studies determined that prophylactic AEDs tended to prevent postoperative seizures, but the effect was not statistically significant.[19] A recent Cochrane systematic review found insufficient high-quality evidence to draw any definitive conclusion about the effectiveness of prophylactic AEDs in this setting.[20] A randomized trial, published after the Cochrane review, assigned patients undergoing craniotomy for glioma or metastases to either 7 days of phenytoin or no seizure prophylaxis. Although the study was likely underpowered, the incidence of seizures in the 30 days following surgery was 10% in the phenytoin group and 8% in the group that did not receive prophylaxis ($P>.99$).[21] This finding also calls into question the potential benefit of AED prophylaxis for patients undergoing craniotomy.

In 2000, the Quality Standards Subcommittee of the American Academy of Neurology reviewed the evidence concerning the efficacy of prophylactic AEDs in patients with all brain tumor types.[22] Because the numbers of patients in the studies reviewed were small, they performed a meta-analysis of the 4 available randomized studies that addressed this issue. They concluded that the evidence did not show a benefit from prophylactic AED use and recommended that these drugs not be administered as a standard practice. More contemporary systematic reviews of the published literature have reached the same conclusion.[23,24] An ongoing, randomized, double-blind, placebo-controlled trial is expected to provide definitive data regarding the benefit of prophylactic AED administration for patients with newly diagnosed glioblastoma (NCT01432171). Following surgical resection, patients who have not experienced seizures are randomly assigned to lacosamide or placebo and then observed for up to 1 year. The primary endpoint is time to first seizure. Results are expected in 2017.

Side Effects and Drug Interactions

AED use has been traditionally associated with many unpleasant adverse effects. Approximately 20%–25% of glioma patients treated with phenytoin who undergo cranial irradiation develop rash[25] and, rarely, Stevens-Johnson syndrome.[26] Stevens-Johnson

Table 1. Studies of antiepileptic drug prophylaxis in patients with brain tumors

Study	Total No. Patients	No. Patients on AEDs	Outcome	Comments
Retrospective studies				
Boarini *et al.*[199]	71	33	Odds ratio for seizure 0.41 (95% CI, 0.14–1.19). No patients with therapeutic AED levels had seizures; 18% of untreated patients did.	None
Moots *et al.*[200]	36	4	No seizures in AED group compared with 31% in untreated patients ($P = .60$).	None
Mahaley and Dudka[201]	59	Unreported	Odds ratio for seizure 1.63 (95% CI, 0.52–5.14)	None
Prospective studies				
Franceschetti *et al.*[202]	63	41	Odds ratio for seizure in the AED group 0.36 (95% CI, 0.07–1.76).	AEDs included phenytoin and phenobarbital.
Forsyth *et al.*[203]	100	46	Odds ratio for seizure in the AED group was 0.82 (95% CI, 0.33–2.01).	Median follow-up period of 5.4 months. This study had a high noncompliance rate (45% of patients had low AED levels).
Glantz *et al.*[16]	74	37	Odds ratio for seizure in the AED group was 1.7 (95% CI, 0.6–4.6).	This was a prospective, placebo-controlled, randomized study of valproic acid.
North *et al.*[204]	81	42	Odds ratio for seizure in the AED group was 1.85 (95% CI, 0.56–6.12).	This was a prospective, non–placebo-controlled, randomized study of phenytoin.

Abbreviation: AED, antiepileptic drug.

Table 2. Selected non–enzyme-inducing antiepileptic drugs that are frequently used in brain tumor patients

Drug	Dose Frequency	Route	Notable Side Effects	Primary Metabolism	Need for Level Monitoring?	Titration Rate
Gabapentin	TID	p.o.	Sedation with rapid titration, ataxia, weight gain	Renal	No	Slow
Lacosamide	BID	p.o./i.v.	Dizziness	Mixed	No	Slow
Lamotrigine	BID	p.o	Drug rash, Stevens-Johnson syndrome	Hepatic	Not routinely	Extremely slow
Levetiracetam	BID	p.o./i.v.	Agitation, aggression, psychosis	Unknown	No	Rapid
Pregabalin	BID-TID	p.o.	Sedation, weight gain, thrombocytopenia	Renal	No	Slow
Topiramate	BID	p.o.	Weight loss, cognitive impairment, paresthesias, metabolic acidosis, renal calculi	Mixed	No	Slow
Valproic acid	TID	p.o./i.v.	Hair loss, easy bruising, thrombocytopenia, weight gain, hyperammonemia, tremor, pancreatitis, Parkinsonism	Hepatic	Yes	Rapid

Abbreviations: BID, 2 times daily; TID, 3 times daily.

syndrome has also been described in glioma patients receiving carbamazepine,[27] and patients receiving phenobarbital have an increased incidence of shoulder-hand syndrome.[28] Additional AED side effects include sedation, dizziness, nausea, vertigo, ataxia, cognitive impairment, myelosuppression, and liver dysfunction, many of which appear to be more common in brain tumor patients. Overall, 24% of brain tumor patients on AED therapy experience side effects severe enough to warrant a change or discontinuation of AED therapy.[22] Although carefully controlled studies are lacking, newer AEDs such as levetiracetam, lamotrigine, pregabalin, and lacosamide have more favorable adverse effect profiles, as noted below.

The majority of older AEDs also have clinically significant interactions with other drugs commonly used for brain tumor patients. Phenytoin induces hepatic metabolism and significantly reduces the half-life and bioavailability of dexamethasone.[29,30] Conversely, dexamethasone may also reduce phenytoin levels.[31] Some chemotherapeutic agents commonly used in brain tumor patients, including carmustine (BCNU), reduce phenytoin levels.[32] Additionally, some AEDs induce the cytochrome P450 (CYP450) enzyme system and markedly accelerate the metabolism of several chemotherapeutic agents including nitrosoureas,[33] irinotecan,[34] and erlotinib.[35] Consequently, the optimal doses of these chemotherapeutic agents for patients taking enzyme-inducing AEDs are frequently higher and less predictable than in patients not taking AEDs.

Selecting an Antiepileptic Drug

No published data suggest differential efficacy of one AED over another in the brain tumor population.[15] Hence, AED selection should be based on side effects, drug interactions, convenience, availability, and cost. In current neuro-oncological practice in the United States, older enzyme-inducing AEDs such as phenytoin, carbamazepine, and phenobarbital are rarely used. One of the most frequently prescribed AEDs is levetiracetam, which has no known drug-drug interactions, may be initiated at a therapeutic dose, does not require blood level monitoring, has oral and intravenous formulations, is well tolerated by most patients, and is affordable because of its generic status. Lacosamide shares many of levetiracetam's favorable properties and is gaining popularity as a result.[36] Levetiracetam-lacosamide combination therapy is also safe and feasible for brain tumor patients with refractory seizures. Other agents that are often prescribed include valproic acid and lamotrigine. Valproic acid is an inhibitor of the CYP450 system and thus may increase chemotherapy toxicity. The benefits of lamotrigine are limited by the need to slowly escalate the dose in an effort to minimize the risk of severe skin toxicity. Table 2 summarizes AEDs used in brain tumor patients.

Antiepileptic Drugs and Possible Antitumor Activity

Recent data suggest that valproic acid has antiglioma effects distinct from its anticonvulsant properties. A histone deacetylase inhibitor, valproic acid may function as a radiosensitizer.[37] A retrospective report found that the addition of valproic acid to standard therapy with radiation and temozolomide may prolong survival for patients with newly diagnosed glioblastoma.[38] Similar findings were reported in a post hoc analysis from the definitive clinical trial that established temozolomide as a standard-of-care for glioblastoma.[39] However, the published studies suffer from several limitations, and the benefit from valproic acid is not consistently demonstrated.[40] A randomized trial may be needed to settle this question.[41] Valproic acid decreases temozolomide clearance by 5%, but the clinical relevance of this finding is unknown.

Corticosteroids: Use and Complications

Almost all patients with brain tumors receive corticosteroids at some point in the course of their disease. Steroids help control peritumoral vasogenic edema and alleviate accompanying signs and symptoms. They also have antiemetic and analgesic effects and improve appetite and mood.[42,43] In lymphoma and leukemia, steroids exert oncolytic effects and are utilized as part of the treatment regimen. The effects of steroids on neuroimaging are relevant to response criteria in high-grade gliomas; both RANO and Macdonald criteria require patients to be off steroids or on stable doses for response evaluation.[44,45]

There are no standardized guidelines for the timing, dose, duration, and taper schedule of steroids despite their widespread use in neuro-oncology. An individual patient's steroid

requirements may differ depending on lesion size and location, mass effect, and symptoms. Patients are often started on steroids at diagnosis and continue to receive them through surgery and chemoradiation and sometimes even after treatment because of the symptomatic benefit.

Dexamethasone is often preferred due to its lack of mineralocorticoid activity, although prednisone and methylprednisolone have also been used. Dexamethasone has a biological $t_{1/2}$ of 36–54 hours and thus provides symptomatic benefit for a prolonged period. As such, despite the tendency for administration every 6 hours or 4 times daily, it can generally be given in more convenient twice-daily administration. The conventional starting dose is 16 mg/day.[46,47] Recent studies have indicated that lower starting doses suffice in selected patients.[46] Vecht at al evaluated patients with brain metastases who were randomized to receive daily doses of 4, 8, or 16 mg of dexamethasone.[48] After 1 week of treatment, there was no difference in improvement between 4 and 16 mg as long as there was no evidence of impending brain herniation.

The duration of steroid use and taper schedule in clinical practice is arbitrary and often clinician or institution dependent and symptom dependent. In one prospective study, 29% of high-grade glioma patients were able to taper off steroids 3 months post radiation.[49] In another study, only 21% of patients tolerated steroid taper. In both studies, 55%–58% of patients required an increase in dose during radiation.[50] Headache was the most common symptom requiring steroid increase (34%–41%). Better performance status was associated with successful early taper. Patients with primary brain tumors tend to remain on steroids for a longer time (23 weeks) than those with secondary brain tumors (7 weeks).[51] In the aforementioned Vecht study, patients who were on 4 mg required a slower taper and often needed reinstitution of steroids after discontinuation. Twice-daily dexamethasone taper during radiation for brain metastases was found to be effective in one study, in which 13 of 14 patients remained off steroids at 30 days post radiation.[52] Analyses of various cooperative group trials have all indicated that baseline corticosteroid use in glioblastoma is negatively associated with survival.[53–55] In general, every effort should be made to start steroids at low doses and taper as quickly as possible.

A recent review and clinical practice guideline for brain metastases suggested that dexamethasone be started at 4–8 mg/day for mild symptoms or 16 mg/day for severe symptoms from mass effect, with an attempt to taper slowly over 2 weeks or longer in symptomatic patients.[56]

Unfortunately, the side effects of corticosteroids limit their long-term use. The incidence of toxicity is related to cumulative dose and duration of treatment. Most studies have shown that steroid-related side effects occur frequently in patients using dexamethasone 16 mg/day for more than 2–3 weeks.[47,48,51,52,57]

Corticosteroid side effects may be neurological or nonneurological. Myopathy is a common neurological side effect and typically produces proximal extremity weakness (particularly in the legs) and, in severe cases, neck flexor and respiratory muscle weakness. The frequency of steroid-induced myopathy in cancer patients ranges from 2% to 60%.[47,51,57,58] Although most studies indicate that the development of steroid myopathy is dose and duration dependent, one study found that steroid myopathy can develop rapidly and is related to the cumulative dose.[57] Steroid myopathy is a clinical diagnosis; patients have proximal weakness with normal sensation and preserved deep tendon reflexes. Serum muscle enzymes are normal. Electromyography may be normal or show findings suggestive of myopathy. Treatment involves tapering or discontinuing steroids along with physical therapy; recovery usually takes weeks to months.

Mood disorders, psychosis, delirium, and memory loss are also corticosteroid side effects. More common are anxiety, insomnia, euphoria, irritability, and emotional lability. Depression is uncommon. Some patients develop mania, most commonly women and those with a history of psychiatric illness. Steroid psychosis, including hallucinations or delirium, may also occur. Discontinuation of steroids leads to resolution of symptoms. Occasionally, patients may require neuroleptics, lithium, or valproic acid. Tricyclic antidepressants are not recommended. Steroid-induced neuropsychiatric symptoms must be distinguished from psychiatric or metabolic disorders. Hiccup is another dose-related idiosyncratic effect of corticosteroids and may respond to dose reduction or agents such as phenothiazines and baclofen.

Systemic complications of corticosteroid use may involve almost any organ system, and space limitations preclude a thorough review; infectious aspects are discussed elsewhere in this manuscript. The association of peptic ulcer disease and steroid use is controversial.[59,60] Some studies have shown that patients on both corticosteroids and nonsteroidal anti-inflammatory drugs have a higher risk of gastrointestinal bleeding.[61–64] Despite a paucity of supporting literature, many patients receiving corticosteroids are prescribed histamine receptor (H2) blockers or proton pump inhibitors. High-dose steroids are also associated with a risk of colonic perforation, which usually affects the sigmoid colon.[65–67] Patients may present with an acute abdomen or have an insidious course due to masking of signs and symptoms by the anti-inflammatory effects of steroids. Endocrine side effects include Cushing's syndrome and hyperglycemia, which are usually reversible after steroid discontinuation. In patients with pre-existing diabetes, the insulin requirement may increase. Adrenal insufficiency or steroid withdrawal syndrome may occur when patients on long-term steroids undergo a rapid taper. Patients may present with headache, nausea, anorexia, malaise, myalgia, arthralgias (pseudorheumatism), and low-grade fever.[68–70]

Metabolic effects of corticosteroids on bone are another cause of steroid morbidity. Osteoporosis, leading to fractures of the spine and hip, is not rare. Bone loss is likely related to reduced calcium absorption, secondary hyperparathyroidism, and decreased sex hormones. Calcium and vitamin D supplements in standard doses are recommended for prevention. Oral bisphosphonates may be used, but there is a risk of increased peptic ulcer disease, especially in conjunction with corticosteroids. Kyphoplasty may be helpful for compression fractures. Avascular necrosis of the hip should be considered in a patient with hip pain on steroids.

A medication that controls vasogenic edema without corticosteroid side effects would be of great value. Bevacizumab has substantial steroid-sparing effects; a majority of patients in the BRAIN trial were able to lower their steroid doses, and the reductions were often substantial.[71] Tyrosine kinase inhibitors (TKIs) potently targeting vascular endothelial growth factor receptor 2 (VEGFR-2), such as cediranib and cabozantinib, have also shown steroid-sparing effects in clinical trials but are not utilized clinically for this purpose. Corticorelin acetate, a synthetic formulation of human corticotropin-releasing factor, is also under study with promising steroid-sparing effects on edema.[72]

Venous Thromboembolism

Brain tumors confer a high risk for venous thromboembolic (VTE) disease, both during and beyond the perioperative period. This has been best studied in high-grade glioma, where it is estimated that 3%–20% of patients develop perioperative deep venous thrombosis (DVT) or pulmonary embolism (PE), depending upon prophylaxis and type of screening.[73] In fact, radiolabeled fibrinogen scans have shown DVTs in 60% of postoperative glioblastoma patients.[74] An elevated risk persists beyond the perioperative period; cumulative incidence at 6 months is 17%[75] and ~20% at 1 year.[76,77] Table 3 summarizes risk factors for VTE development. The high incidence of VTE should translate into a correspondingly low threshold for pursuing lower extremity Doppler studies or CT pulmonary angiogram in patients with lower extremity edema, calf discomfort, dyspnea, chest pain, or other cardiopulmonary symptoms. Upregulation of tissue factor and its downstream effectors appears to play a key role both in activation of clotting pathways and oncogenic signaling mechanisms important for cancer progression. The interested reader is referred elsewhere for in-depth discussion of the pathophysiology of hypercoagulability in neuro-oncology patients.[73,78,79]

Management of VTE in neuro-oncology patients is influenced by concerns of precipitating intratumoral hemorrhage with anticoagulant administration. Large case series have shown anticoagulation to be effective and acceptably safe in high-grade gliomas[80–82] as well as brain metastases.[83] Metastases from lung and breast tumors have a relatively low incidence of spontaneous hemorrhage and should not be seen as a strong contraindication to anticoagulation. Anticoagulation is often avoided in tumors with a particularly strong tendency towards hemorrhage such as melanoma and renal cell carcinoma, although selected patients with brain metastases from melanoma have been safely anticoagulated for VTE.[84] Thus, the presence of a nonhemorrhagic brain tumor is not a strong contraindication to anticoagulation. Noncontrast head CT, to exclude more than petechial hemorrhage, may serve as a useful risk stratification approach.[85]

The alternative to anticoagulation is placement of an inferior vena cava (IVC) filter. No prospective studies have compared IVC filters to anticoagulation in any patient population. However, case series have reported unacceptable outcomes with IVC filters in a mixed population of brain tumor patients, with a 12% incidence of recurrent PE along with a 57% incidence of postphlebitic syndrome, recurrent DVT, or IVC/filter thrombosis;[81] fatal PE despite IVC filter is well documented.[86] Consequently, we restrict their use to patients with VTE and strong contraindications to anticoagulation, such as recent intracranial surgery or hemorrhage. Little evidence supports combined therapy with anticoagulation and IVC filter.[87]

Several options for anticoagulation exist (Table 4). Choices for initial therapy include low molecular weight heparin (LMWHs) or unfractionated heparin; LMWHs are generally preferred, with unfractionated heparin being reserved for symptomatic PE, renal insufficiency, or patients at high risk for bleeding.[79] For chronic therapy, FDA-approved agents include warfarin and LMWH. While both are effective, LMWHs avoid the need for frequent laboratory monitoring and the potential drug-drug interactions with warfarin that phenytoin, trimethoprim/sulfamethaxole, omeprazole, and other commonly prescribed medications pose. LMWH was markedly superior to warfarin at preventing recurrent VTE in cancer patients in general, although no study restricted to neuro-oncology patients has been performed.[88] The newer oral agents that inhibit thrombin or factor Xa are not well studied to date in cancer patients. Duration of anticoagulation should be individualized based on the patient's risk factors. Three to 6 months represent a minimum duration for anticoagulation, and patients with active malignancy or ongoing chemotherapy should be considered for prolonged therapy. Thus, lifelong anticoagulation is a consideration for the glioblastoma patient.[73]

The high incidence of VTE has led to interest in prophylaxis. The benefits of VTE prophylaxis in the perioperative setting have been clearly demonstrated; a large study, which randomized more than 300 patients (almost all of whom had brain tumors) to

Table 3. Risk factors for venous thromboembolism in glioma

Patient Factors
Age (especially >75 y)
ABO bloodtype (A, AB)
Prior deep vein thrombosis or pulmonary embolism
Leg paresis, prolonged immobility
Multiple medical comorbidities
Obesity
Glioma-associated factors
Tumor grade (high > low-grade glioma)
Intraluminal thrombosis in surgical specimen
Recurrent disease
Tumor size (>5 cm)
Postoperative residual disease (biopsy>partial>gross total resection)
Treatment-associated factors
Postoperative period
Chemotherapy
Anti-VEGF treatment
Hormonal therapy
Venous access device

Abbreviation: VEGF, vascular endothelial growth factor.
Adapted with permission from Perry JR. Thromboembolic disease in patients with high-grade glioma. Neuro-Oncol 2012 (suppl 4):iv73-iv80.

Table 4. Treatment of venous thromboembolism in patients with brain tumors

Acute Treatment	Chronic Treatment
• UFH: 80 U/kg i.v. bolus, then 18 U/kg per hour i.v., dose adjusted based on aPTT • Dalteparin: 200 U/kg once daily or 100 U/kg, every 12 h (mo1) • Enoxaparin: 1.5 mg/kg once daily or 1 mg/kg every 12 h • Tinzaparin: 175 U once daily	• Warfarin: adjusted based on INR • Dalteparin: decrease to 150 U/kg once daily (mo 2–6) • Enoxaparin: 40 mg, daily, 1.5 mg/kg once daily or 1 mg/kg every 12 h • Tinzaparin: 175 U once daily

Abbreviations: INR, international normalized ratio; aPTT, activated partial thromboplastin time; mo, months.
Reprinted with permission of Jo JT et al.[79]

compression stockings ± enoxparin 40 mg daily on postoperative day 1, halved the rate of VTE without increasing bleeding.[89] Long-term primary prophylaxis outside the perioperative period has been studied in high-grade glioma. The PRODIGE study randomized patients to dalteparin versus placebo. The study was terminated early because of drug supply issues. While a trend towards reduced VTE was seen in the dalteparin arm, intracranial hemorrhage was more frequent (5% vs 1%). Thus, primary prophylaxis is not advised at present.[75] A biomarker-based scale to predict risk of VTE with newly diagnosed high-grade glioma has been proposed and warrants validation.[90]

Adverse Events with VEGF/VEGFR Targeting Agents

Angiogenesis is a characteristic feature of aggressive malignancies, including many brain tumors.[91] We will focus on the use of inhibitors of VEGF signaling, as this is the most prominent mediator of tumor-associated angiogenesis.

Over the past several years, evaluation of antiangiogenic agents has been a highly active area of clinical research in neuro-oncology and culminated in the FDA's accelerated approval of bevacizumab, a humanized, recombinant in recurrent glioblastoma patients was further heightened by a recent phase II study demonstrating significantly improved outcome when bevacizumab was combined with lomustine compared with either agent alone.[93] However, the role of bevacizumab in newly diagnosed glioblastoma patients remains unclear following data from 2 recently reported randomized, placebo-controlled phase III trials that demonstrated improved progression-free survival but failure to improve overall survival and mixed results in quality-of-life evaluations.[94,95]

Interest in the use of bevacizumab for indications other than glioblastoma has expanded in the past few years. Although randomized phase III trials have not been performed, single arm phase II studies have supported the use of bevacizumab for recurrent grade III malignant glioma patients.[96–99] Retrospective series have also demonstrated encouraging benefit associated with bevacizumab therapy in patients with vestibular schwannoma and neurofibromatosis type 2,[100] meningioma,[101,102] ependymoma,[103] hemangioblastoma,[104] and some metastatic CNS tumors.[105–107] Moreover, it is a potent agent against symptomatic radiation necrosis.[108]

In addition to bevacizumab, a variety of other antiangiogenic agents has been investigated for malignant glioma patients including TKIs targeting VEGFR (monoclonal antibodies that block VEGF binding to VEGFR) and a soluble decoy VEGFR. The use of these agents has become widespread in oncology because many are approved for a variety of cancer indications. The spectrum of toxicities associated with agents that block VEGF/VEGFR signaling is thus now well established. Therapeutics with additional targets, such as many VEGFR TKIs, are typically associated with broader toxicity profiles. We will summarize the aggregate adverse event experience associated with bevacizumab as the prototypical inhibitor of VEGF/VEGFR signaling. Two main categories of adverse events emerge from this experience: those that are common and typically mild and those that are uncommon and often severe.

Common/Often Mild Adverse Events

Fatigue, hypertension, and proteinuria occur frequently in bevacizumab recipients, although the severity is generally mild. Fatigue, the most common adverse event associated with VEGF/VEGFR inhibitors, is low grade and manageable in most cases. Among recurrent glioblastoma patients on the AVG3708g study, 45% of patients experienced fatigue of any grade, while grade ≥ 3 fatigue was reported in 3.6% and 8.9% of those treated with bevacizumab and bevacizumab plus irinotecan, respectively.[109] Adding bevacizumab to adjuvant temozolomide in newly diagnosed glioblastoma patients increased grade ≥ 3 fatigue frequency modestly compared with placebo (13.1% and 9.0% on Radiation Therapy Oncology Group [RTOG] 0825 and 7.4% and 4.7% for AVAglio).[94,95]

Hypertension with VEGF/VEGFR therapy is linked with both patient-related factors (eg, age, comorbidities, lifestyle factors) and concurrent medications as well as drug-related factors including agent, dose, and schedule. A recent meta-analysis demonstrated that 55% of bevacizumab recipients developed a >10 mmHg increase in systolic blood pressure (SBP) or > 5 mm Hg increase in diastolic blood pressure (DBP); 7.6% developed either a > 40 mmHg SBP increase or > 20 mmHg DBP increase, and 0.12% developed hypertensive crisis.[110] Hypertension of any grade has been reported in 36%–39% of glioblastoma patients, while grade ≥ 3 hypertension affects 4%–11% of patients.[94,95,109] Recent reviews provide guidance on monitoring and treatment of hypertension in patients treated with VEGF/VEGFR inhibitors.[111,112]

Proteinuria develops due to inhibition of VEGF-mediated maintenance of podocyte-endothelial cell integrity of normal glomerular capillaries and the subsequent development of a thrombotic microangiopathy.[113] Hypertension increases the risk of proteinuria.[114] Up to 63% of cancer patients treated with bevacizumab develop grade 1–2 proteinuria, while grade 3–4 proteinuria has been reported in 1%–15%.[115] Proteinuria of any grade has been noted in up to 16% of glioblastoma patients, with 1%–3% developing grade ≥ 3 proteinuria.[95,109] Current management guidelines include regular prospective urinalysis monitoring, early referral of patients with more severe proteinuria for nephrology consultation, and interruption of dosing.[115] Angiotensin-converting enzyme inhibitors and angiotensin 2-receptor antagonists can provide a renoprotective effect that may reduce proteinuria and help control blood pressure.[116]

Dysphonia or hoarseness affects up to 37% of patients treated with VEGF/VEGFR inhibitor therapy.[117] Management considerations include fiberoptic laryngeal examination and discontinuation of antiangiogenic therapy.

Less Common/Often Severe Adverse Events

Anti-VEGF/VEGFR therapy has been reported to increase the risk of cancer-associated hypercoagulability. A recent meta-analysis demonstrated a relative risk of 1.33 for VTE in oncology patients treated with bevacizumab compared with controls,[118] although other such studies have been negative.[119] Among general oncology patients with VTE, systemic anticoagulation administered with ongoing bevacizumab therapy has been associated with a low (<1%) hemorrhage risk[119]; however, a recent retrospective analysis noted an 11% rate of intracranial hemorrhage in

bevacizumab patients receiving concurrent anticoagulation compared with only 3% of those on bevacizumab without anticoagulation.[120] Grade ≥ 3 VTE and arterial thromboembolism (ATE) occurred in 3.6% and 2.4% of recurrent glioblastoma patients, respectively.[109] In newly diagnosed glioblastoma patients, grade ≥3 VTE occurred with similar frequency (7%–10%) in bevacizumab and placebo recipients.[94,95] In contrast, the frequency of grade ≥ 3 ATEs was clearly higher in bevacizumab recipients (5.0% vs 1.3%).[94,95] Additional bevacizumab administration is contraindicated following ATEs, while bevacizumab may be continued with careful monitoring for patients with VTEs who are appropriately anticoagulated.

Bevacizumab increases the risk of hemorrhage in oncology patients. Grade 3 bleeding occurred in 3.5% of 12 617 cancer patients treated across 20 randomized trials, with a 2.48 relative risk for bevacizumab recipients compared with controls.[121] Approximately 35% of glioblastoma patients experience bleeding of any grade,[94,95] with grade ≥ 3 hemorrhage limited to 1%–2%.[94,95,109] The overall intracranial hemorrhage (ICH) rate among cancer patients treated with bevacizumab is 0.3%–0.9%[122,123] and increases to 0.9%–1.5% in those with known primary or metastatic brain tumors.[123,124] ICH of any grade affects 1%–3% of glioblastoma patients treated with bevacizumab, while grade ≥ 3 ICH occurs in 0.6%–2%.[95,109,125] Of note, spontaneous ICH of any grade and grade ≥ 3 without bevacizumab occur in 2% and 0.9%, respectively.[95,109] Further bevacizumab dosing is contraindicated for oncology patients who develop ICH.

Bevacizumab appears to increase the risk of ischemic stroke above a baseline spontaneous level that occurs in high-grade glioma patients. A recent meta-analysis of glioma patients noted a 1.8% rate of ischemic stroke that increased to 6.2% for bevacizumab recipients.[126] Another recent series noted a 1.9% rate of ischemic stroke in glioblastoma patients treated with bevacizumab, which appeared to be associated with prolonged use.[125]

Posterior reversible encephalopathy syndrome is a rare, clinicoradiological entity that has been linked with multiple therapies including antiangiogenic agents.[127,128] Most patients recover with acute intervention including blood pressure control, AEDs, and treatment of cerebral edema. Reintroduction of bevacizumab is generally contraindicated following this complication.

Wound-healing complications have been reported in oncology patients during bevacizumab therapy.[129] For this reason, a 4-week minimum window is recommended between bevacizumab and surgery, both prior to and following craniotomy. In a recent retrospective study, patients who received bevacizumab prior to repeat craniotomy had a 35% incidence of wound-healing complications compared to 10% in patients who had not received bevacizumab.[130] Among recurrent glioblastoma patients treated with bevacizumab, wound dehiscence of any grade and grade ≥3 occurred in 4.2% and 1.8%, respectively.[109] Among newly diagnosed glioblastoma patients, wound-healing complications were more frequent in bevacizumab recipients compared with controls (any grade, 6.9% vs 4.7%; grade ≥ 3, 3.3% vs 1.6%).[95]

Most large series report gastrointestinal perforation in 0%–3% of oncology patients treated with bevacizumab.[131–133] Gastrointestinal perforation has been reported in 0.8%–1.7% of glioblastoma patients treated with bevacizumab.[94,95,109] Corticosteroids may mask acute symptoms. Medical management is the initial treatment of choice, but early surgical consultation is warranted for prompt intervention as indicated.

The impact of antiangiogenic agents on cognition remains unclear. Recent data have demonstrated a detrimental impact of bevacizumab on some areas of cognitive function in newly diagnosed glioblastoma patients.[94] In contrast, the same battery of cognitive evaluation revealed stable to improved cognitive function in more than 70% of recurrent glioblastoma patients treated with bevacizumab.[134] Furthermore, cognitive decline has not been linked to anti-VEGF/VEGFR therapy in other malignancies. This important issue requires further investigation.

Hematological Toxicity from Chemotherapy

While hematological toxicity of standard adult brain tumor therapy is generally less common and milder than for many other malignancies, it remains a highly pertinent issue for clinicians. Profound anemia is rare with temozolomide but is slightly more common with nitrosourea-based regimens. High-grade lymphopenia is very common with dose-dense temozolomide regimens and corticosteroid use and predisposes to pneumocystis and other infections (vide infra). Neutropenia is relatively uncommon with temozolomide but fairly common with nitrosoureas. With temozolomide, myelosuppression in general is approximately twice as common in women than in men.[135,136] The addition of bevacizumab to temozolomide increases the risk of grade 3+ neutropenia from 3.7% to 7.2% and grade 3+ thrombocytopenia from 7.7% to 10.2%.[94] Table 5 summarizes the frequency of high-grade hematological toxicity with common regimens.

The management of acute hematological toxicity in brain tumor patients is drawn from medical oncology, with standard guidelines applicable for decisions regarding use of red blood cell transfusions and colony-stimulating factors. The possible exception is in the prophylactic management of thrombocytopenia. ASCO guidelines recommend a threshold of 10 000 platelets for prophylactic transfusion in solid tumors. However, these guidelines note it may be appropriate to raise the threshold to 20 000 for patients with necrotic tumors that are at increased risk of hemorrhage, and that in some patients a risk of major bleeding of 2%–5% might suffice to use a trigger of 20 000. There is an absence of data derived from the brain tumor population. It would seem reasonable to set an even higher threshold for a patient with an already-hemorrhagic brain tumor. Fever, sepsis, and the rapidity of platelet count drop should also be considered when a threshold is set for an individual patient. For neurosurgical intervention, it is recommended that patients have at least 100 000 platelets.

The use of alkylating agents has also been associated with long-term hematological toxicity. The risk of aplastic anemia is estimated at 1 per 10 000 patients exposed to temozolomide; 17 cases of leukemia and 7 cases of myelodysplastic syndrome were reported between 1999 and 2008. How temozolomide compares with other alkylating agents regarding the risk of secondary leukemias and prolonged or permanent bone marrow failure remains unknown.[136,137]

Infections

Multiple factors conspire to predispose neuro-oncology patients to CNS and systemic infections.[138] Neurosurgical procedures

Table 5. Hematological toxicities of commonly utilized brain tumor chemotherapies

	Grade 3 (ANC 500–1000; Platelets 25 000–50 000; Hemoglobin < 8.0)	Grade 4 (ANC < 500; Platelets < 25 000)
Temozolomide		
Thrombocytopenia	3% (concomitant phase), 11% (adjuvant phase)[205]	
Neutropenia	4% (concomitant phase), 4% (adjuvant phase)[205]	
Lymphopenia	12% (adjuvant)[206]	3% (adjuvant)[206]
Anemia	1% (concomitant), 1% (adjuvant)	
PCV (standard)		
Thrombocytopenia	14%	7%
Neutropenia	24%	8%
Anemia	6%	1%
BCNU[207]		
Thrombocytopenia	32%	
Neutropenia	26%	
CCNU[208]		
Thrombocytopnia	25%	
Neutropenia	20%	

Abbreviations: ANC, absolute neutrophil count; PCV, procarbazine/CCNU/vincristine.

create barrier disruption, while chemotherapy and corticosteroids contribute to impairment of cell-mediated immunity and occasional neutropenia. Poor nutritional status is another likely contributor. The risk of a surgical site infection following craniotomy is 2%–3%. Several groups have found that using carmustine wafers increases this risk;[139,140] a recent case-control study reported an odds ratio of 6.7 for surgical site infection with their use,[141] although others have disputed this point.[142]

Immunosuppression is an important cause of infections, particularly outside the perioperative period. Neutropenic fever is uncommon with standard neuro-oncology regimens and will not be discussed further because its management does not differ from other populations. Impairment of cell-mediated immunity, in contrast, is particularly germane to brain tumor patients.

Even prior to the use of temozolomide, neuro-oncologists recognized that corticosteroid use predisposes to *Pneumocystis jirovecii* pneumonia (PCP) and that lymphopenia is a key risk factor.[143,144] The phase II trial that served as the forerunner to the "Stupp regimen" (incorporating daily temozolomide with radiation) reported that 79% of patients developed grade 3+ lymphopenia and 2 of their first 15 patients (both lymphopenic) developed PCP; PCP prophylaxis was subsequently given to all patients.[145] A study in melanoma patients found that 60% developed lymphopenia with CD4 counts preferentially affected while on a dose-dense schedule akin to the Stupp regimen; since these patients were generally not on corticosteroids, dose-dense temozolomide was clearly the culprit.[146] The recommendation to give PCP prophylaxis to patients being treated with radiation and temozolomide is part of the package insert. Clear guidelines for when prophylaxis may be safely discontinued are lacking; a recent publication suggested giving prophylaxis to patients on chronic steroids and patients receiving temozolomide with lymphocyte counts ≤ 500, although this approach has not been prospectively validated.[147] Because PCP is not rare in other brain tumors treated with chemotherapy and corticosteroids (eg, primary CNS lymphoma), it is prudent to follow lymphocyte counts and consider prophylaxis as well.[148] The clinician has a choice of several regimens.[147]

Reactivation of herpesviruses has been seen with temozolomide, and disseminated zoster and CMV have also been reported.[149] CMV pulmonary, colonic, and hepatic infections have been reported[150] and are treatable with antiviral therapy. Prophylaxis with acyclovir may prevent zoster.[151] Other rare infections associated with temozolomide and dexamethasone include aspergillus,[152] disseminated strongyloides,[153] bronchopulmonary infection with *Bordatella bronchiseptica* (a cause of "kennel cough"),[154] cryptococcal meningitis,[155] disseminated tuberculosis,[156] and hepatitis B reactivation.[157–159]

Rituximab, a monoclonal antibody targeting the protein CD20 expressed on the surface of B lymphocytes, is commonly incorporated into CNS lymphoma therapy. Rituximab has been linked to reactivation of hepatitis B virus,[160] and antiviral prophylaxis may be indicated.[161] Hepatitis C virus reactivation has also been reported. Numerous cases of progressive multifocal leukoencephalopathy have been seen following rituximab use in other disorders,[162] and it is likely only a matter of time until this is reported in primary central nervous system lymphoma.

Endocrine and Fertility Issues

The incidence of radiation-induced damage to the hypothalamic-pituitary axis in adults is uncertain but may exceed 30% when the hypothalamus and pituitary are in the radiation field.[163] The hypothalamus is more sensitive than the pituitary gland. Risk factors include increasing total dose and dose per fraction and age (children and young adults are the most vulnerable). Endocrine dysfunction typically starts within a few years of radiation. In adults, the growth hormone axis is most sensitive to radiation; manifestations of growth hormone deficiency include fatigue, altered body composition, decreased bone mineral density, and increased cardiovascular mortality. Gonadotropin deficiency may manifest as oligomenorrhea/amenorrhea or low testosterone. Adrenocorticotropic hormone deficiency is less common and may require hydrocortisone replacement therapy. Mild hyperprolactinemia may also be a consequence. This topic is comprehensively reviewed elsewhere.[163]

Preservation of fertility represents an important concern for brain tumor patients and is especially complex in young women. Alkylating agents are the most gonadotoxic chemotherapy drugs.[164] The incidence of infertility in brain tumor patients is poorly studied. Alkylating drugs cause follicular depletion and destruction of oocytes, commonly resulting in premature ovarian failure. Hormonal abnormalities and alterations in menstrual cycles (amenorrhea or oligomenorrhea) are commonly seen in women treated with radiation and alkylator-based chemotherapy for gliomas in another pilot study.[165] Small pilot studies confirm an at least transient deleterious effect of temozolomide on sperm count, motility, and density in some men.[166]

Although there are case reports of preservation of male[167] and female[168] fertility after temozolomide exposure, discussion of possible fertility preservation must precede initiation of chemotherapy. Cryopreservation of sperm is widely available for men.

Techniques to preserve female fertility include in vitro fertilization, embryo cryopreservation, cryopreservation of unfertilized ova, cryopreservation and transplantation of thawed ovarian tissue, and use of GnRH-a to simulate a prepubertal hormonal environment and decrease the risk of ovarian failure.[164] Preventing conception is recommended in the first 2 years after chemotherapy in women.[164]

Fatigue and Mood

Fatigue is a common symptom in primary brain tumor patients, with 40%–70% reporting fatigue during the course of their illness.[169] The prevalence is even higher in primary brain tumor patients undergoing cranial irradiation, with more than 80% reporting fatigue during treatment.[170] The pathophysiology underlying fatigue is not well understood.

it is often underreported, underdiagnosed, and undertreated.[171] Fatigue is typically assessed through patient self-reporting. History and physical examination, laboratory data, and family members' descriptions of patient behaviors can help supplement patient self-reporting. For use in clinical research, there are well-established questionnaires for fatigue assessment validated in brain tumor patients including the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC-QLQ-C30) fatigue subscale.[172,173] For patients with moderate to severe fatigue, the NCCN guidelines recommend evaluation for treatable contributing factors including pain, medications (eg, anticonvulsants and opioids), emotional distress (eg, depression or anxiety), sleep disturbance, anemia, nutritional deficiencies, decreased functional status, and comorbidities (eg, alcohol/substance abuse, endocrine dysfunction, and infection).[171]

Mood disorders are common in brain tumor patients and may be a treatable cause of fatigue. In glioma, depression can be associated with physical functional impairment, cognitive impairment, higher mortality, increased frequency of medical complications, and reduced work productivity.[174] One longitudinal twin-center study showed that 20% of glioma patients developed major depressive disorder (MDD) in the first 6 months after starting radiotherapy and that MDD was 3–4 times more likely to occur in patients with prior depression or significant functional impairment.[175] However, antidepressants may lower the seizure threshold, impair memory, or cause fatigue.[174] A recent Cochrane meta-analysis found no eligible randomized controlled trials, controlled trials, cohort studies, or case-control studies of the pharmacological treatment for depression in primary brain tumor patients.[174] While antidepressants are effective treatments for depression in a variety of other patient populations and may be indicated in brain tumor patients with MDD, it is unclear which pharmacological intervention is optimal.

Few studies have evaluated pharmacological and/or nonpharmacological interventions for fatigue in brain tumor patients (Table 6), but the literature in the general cancer population is more extensive.[176] Favorable effects on fatigue have been reported with exercise, psychoeducation on self-management of fatigue, and corticosteroids.[176] A meta-analysis found aerobic exercise to be more effective than the control intervention for fatigue during and following tumor-directed therapy, especially in solid tumor patients.[177] However, the optimal type, intensity, and timing of exercise are not known. A recent double-blind, randomized, placebo-controlled study of dexamethasone in 84 patients with advanced cancer revealed a significant improvement in the Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-F) subscale with dexamethasone 4 mg orally twice daily for 14 days.[178] Since many brain tumor patients are already on dexamethasone for management of cerebral edema, it is unclear if increasing the dose of dexamethasone is a meaningful intervention for fatigue.

Several other pharmacological interventions have been studied for fatigue, but there is no class I evidence to support their routine use. Drugs to improve anemia, including erythropoietin and darbepoetin, improve fatigue but cannot be recommended because they are also associated with increased mortality in advanced cancer patients and more adverse events compared with placebo.[179] Studies of psychostimulants in cancer patients, including primary brain tumor patients, have yielded mixed results.[176] A randomized study of modafinil in primary brain tumor patients did not significantly reduce fatigue compared with placebo.[180] Fatigue scores significantly declined compared with baseline assessment in both the modafinil and placebo groups, demonstrating the difficulty of interpreting single-arm studies. Preliminary results from 2 double-blinded, placebo-controlled studies of armodafinil (the *R*-enantiomer of modafinil) for primary brain tumor patients receiving brain irradiation suggest no statistically significant reduction in fatigue.[181,182] However, subgroup analysis of the Shaw et al study suggests that those patients with more baseline fatigue (defined as a fatigue subscale less than median) may experience less fatigue when treated with armodafinil versus placebo.

Sleep disturbances, both insomnia and hypersomnia, can also exacerbate fatigue.[171] Sleep interventions designed to enhance sleep quality are simple interventions that may help patients with fatigue. Examples include stimulus control (getting out of bed after 20 min if unable to fall asleep), sleep restriction (avoiding long or late afternoon naps, limiting total time in bed), and good sleep hygiene (avoiding caffeine after noon, establishing an environment conducive to sleep). Medications such as corticosteroids may also contribute to insomnia. Pharmacological interventions for insomnia have not been tested in a randomized fashion in brain tumor patients, although basic principles for pharmacological management of insomnia have been advocated, including starting with low doses and avoiding long-term use of benzodiazepines.[169]

Neurocognitive Impairment

Impairment of neurocognitive function is very common in brain tumors patients, both as a result of the direct effects of the tumor and its surrounding edema and the sequelae of therapy. As treatments for brain tumors improve and patients live longer, it is likely that these complications will increase in importance, similar to the situation encountered with childhood survivors of brain tumors.[183]

Neurocognitive impairment is very common after radiation therapy. In some studies, more than 90% of patients who survive more than 6 months after receiving whole brain radiation therapy (WBRT) have evidence of neurocognitive impairment.[184] Radiation therapy can cause functional deficits in memory, attention, and executive function and thereby affect the patient's quality

Table 6. Clinical trials of interventions for fatigue in brain tumor patients

Reference	Intervention	Patient Population	Study Design	Assessment of Outcome Measures	Fatigue Outcomes
Boele, et al. *Neuro Oncol* 2013[180]	Modafinil (up to 400 mg/day) vs placebo for 6 weeks, with cross-over after 1-week washout period	37 patients with primary brain tumors and no evidence of tumor recurrence in previous 6 months	Randomized, double-blinded, placebo-controlled study with cross-over	Self-reported questionnaires including CIS for fatigue at baseline, immediately after first treatment period (6 weeks) and immediately after cross-over treatment period (12 weeks)	No significant difference in CIS score for fatigue severity for modafinil vs placebo
Butler, et al. *Int J Radiat Oncol Biol Phys* 2007[209]	d-threo-MPH (5–15 mg BID) vs placebo	68 patients with primary or metastatic brain tumors undergoing brain irradiation	Randomized, double-blinded, placebo-controlled study	Fatigue assessed by FACIT-F subscales at baseline, end of radiation, and 4, 8, 12 weeks after radiation	No significant difference in FACIT-F subscales between groups at 8 weeks after radiation
Gehring, et al. *J Clin Oncol* 2009[210]	7-week cognitive rehabilitation program vs waiting-list control group	140 patients with low-grade and anaplastic gliomas who were clinically stable (no evidence of disease progression)	Randomized, non-blinded study	Battery of neuropsychological tests and self-reported questionnaires at baseline, after 7-week intervention, 6-month follow up. Mental fatigue evaluated by MFI	Statistically significant difference between groups for self-reported measures of mental fatigue ($P = .049$)
Gehring, et al. *J Neurooncol* 2012[196]	IR-MPH 10 mg BID vs SR-MPH 18 mg daily vs modafinil 200 mg daily for 4 weeks	34 patients with primary brain tumors: 11 IR-MPH, 13 SR-MPH, 10 modafinil (planned sample size was 75 total, 25 per group)	Open-label, randomized, pilot study	Cognitive testing and self-reported measures of fatigue including BFI Total, POMS-Fat, POMS-Vig to evaluate fatigue at baseline and after treatment (median = day 30)	Study terminated early due to slow accrual. Patient reported improvements in fatigue but no statistically significant difference between MPH groups and modafinil group
Shaw, et al. *J Clin Oncol* (abstract 9505)[181]	Armodafinil 150 mg/day vs placebo during radiation and 4 weeks after radiation	54 patients with primary brain tumors undergoing brain irradiation	Phase II, double-blinded, placebo-controlled, randomized study	Fatigue assessed by BFI, ESS, FACT, FACT-BR, FACIT-F subscales at baseline, end of radiation, 4 weeks after radiation	Preliminary analysis suggests no statistically significant difference between armodafinil and placebo at any time point
Lee, et al. *J Clin Oncol* (abstract 2004)[182]	Armodafinil 150 mg/day vs placebo during radiation and 2 weeks after radiation	80 patients with glioma undergoing brain irradiation	Randomized, placebo-controlled pilot trial	Fatigue assessment by FACIT-F subscale, BFI, CSF at baseline, day 22, day 43, day 56	Preliminary analysis suggests no statistically significant difference in the 42-day change (baseline vs day 43) between armodafinil and placebo

Abbreviations: BFI Total, Brief Fatigue Inventory; CFS, Cancer Fatigue Scale; CIS, Checklist Individual Strength; ESS, Epworth Sleep Scale; FACIT, Functional Assessment of Chronic Illness Therapy; FACT-Br, Functional Assessment of Cancer Therapy, Brain cancer; IR-MPH, Immediate release methylphenidate; MFI, multidimensional fatigue inventory; MPH, methylphenidate; POMS-Fat, Profile of Mood States Fatigue-Inertia; POMS-Vig, Profile of Mood States Vigor-Activity; SR-MPH, Sustained release methylphenidate.

of life (QOL).[185] Although the underlying mechanisms remain ill-defined, there is increasing evidence that radiation, in addition to its well-known damage to microvessels, induces neuroinflammation with increased infiltration of activated microglia, decreased hippocampal neurogenesis, and altered neuronal function.[186,187] These changes can be partially abrogated by administration of

indomethacin, although the precise mechanisms involved remain to be clarified.[187] More recent studies suggest a potential role of peroxisomal proliferator-activated receptor (PPAR) α and γ agonists as well as renin-angiotensin system (RAS) blockers for preventing radiation-induced neuroinflammation and neurocognitive impairment independent of improved neurogenesis.[185,188] Other strategies to reduce neurocognitive impairment from radiation therapy involve more conformal approaches such as the use of intensity-modulated radiation therapy or proton-beam therapy as well as strategies to spare the hippocampus.[189]

There is also emerging evidence that chemotherapeutic agents (possibly including temozolomide) may affect neurocognitive function by a variety of mechanisms including inhibition of hippocampal neurogenesis, oxidative damage, white matter damage, decreased hypothalamic-pituitary adrenal axis activity, and reduced brain vascularization and blood flow.[190–192]

Patients with neurocognitive impairment can benefit from a detailed evaluation, sometimes including neuropsychological testing. It is important to determine if fatigue and depression are contributing factors and to treat them optimally when they are present. Many medications can contribute to neurocognitive impairment including AEDs, antidepressants, psychotropics, and even corticosteroids. These should be eliminated, if possible, or used at the lowest possible doses. Laboratory tests should be performed to exclude metabolic abnormalities, anemia, primary hypothyroidism, and vitamin B12 deficiency.

Several agents have been evaluated for potential beneficial effects on neurocognitive function. The RTOG conducted a large, placebo-controlled randomized trial evaluating the benefit of memantine, a *N*-Methyl-D-aspartate inhibitor, in patients with brain metastases receiving WBRT (RTOG 0614, NCT00566852).[193] Memantine was started within 3 days of radiotherapy and continued for 24 weeks, and side effects were limited. There was less decline in the primary endpoint of delayed recall in the memantine arm at 24 weeks, although it did not reach statistical significance ($P = .059$). The lack of statistical significance may be partially due to the fact that only 149 of the 508 initially eligible patients were analyzable at 24 weeks because the majority of patients had progressed and died, which resulted in only 35% statistical power. However, the memantine arm had a significantly reduced rate of decline in memory, executive function, and processing speed in patients receiving WBRT, suggesting that it may be of benefit. Whether patients receiving other forms for radiation therapy for different types of brain tumors will have similar benefits remains to be determined in future studies.

Donepezil, an acetylcholinesterase inhibitor, has also been evaluated in brain tumor patients. In an early open-label phase II study of donepezil in irradiated brain tumor patients, neurocognitive functioning, mood, and health-related QOL were significantly improved following a 24-week course of treatment with minimal toxicities.[194] A double blind, placebo-controlled phase III trial of donepezil (5–10 mg/day) was conducted in long-term brain tumor survivors to confirm these favorable results.[195] Although the neurocognitive composite score was not improved in the donepezil arm, there was improvement in verbal memory, working memory, visuomotor and psychomotor performance, and executive functioning, especially in patients with more severe baseline neurocognitive impairment. These results suggest that some long-term brain tumor survivors may benefit from treatment with donepezil, especially if they have severe neurocognitive impairment.

Other agents, such as methylphenidate and modafinil, have been evaluated in small pilot studies of brain tumor patients with a suggestion of benefit, but definitive studies have not yet been performed.[196,197] Given the relatively limited toxicities of these agents, it may be reasonable to consider brief trials of these medications in selected patients. Cognitive rehabilitation and exercise may also be beneficial.[198]

Conclusion

Therapeutic advances against malignant brain tumors (eg, concomitant chemoradiation with temozolomide and the use of bevacizumab) have added complexity and new complications for neuro-oncologists to master. Because optimal supportive care management in these patients promises to improve QOL and perhaps overall survival itself, understanding of these issues is mandatory. Further studies targeting fatigue, mood, and cognitive dysfunction are also of vital importance for improving our patients' well-being.

Ultimately, many patients with malignant brain tumors reach a point in their illness when further antineoplastic treatment is futile and symptom management and end of life care become the priority. The transition to this phase is often gradual and requires sensitive and empathetic conveyance of the tumor and patient's status at each encounter to ease this passage for the patient and family and to foster maintenance of autonomy and dignity.

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