Patient Management Problem—Preferred Responses

Jordi Bruna, MD, PhD; Patrick Y. Wen, MD, FAAN

Following are the preferred responses for the Patient Management Problem in this CONTINUUM issue. The case, questions, and answer options are repeated, and the preferred response is given, followed by an explanation and a reference with which you may seek more specific information. You are encouraged to review the responses and explanations carefully to evaluate your general understanding of the material. The comment and references included with each question are intended to encourage independent study.

In order to obtain CME credits for this activity, subscribers must complete this Patient Management Problem online at www.aan.com/continuum/cme. Upon completion of the Patient Management Problem, participants may earn up to 2 hours of AMA PRA Category 1 Credits™. Participants have up to 3 years from the date of publication to earn CME credits. No CME will be awarded for this issue after April 30, 2018.

Learning Objectives

Upon completion of this activity, the participant will be able to:

- Discuss the optimal medical and neurologic management of patients with high-grade gliomas
- Recognize the most frequent adverse events related to treatments in patients with high-grade gliomas
- Choose the best treatment for patients with high-grade gliomas
- Recognize the pitfalls and advantages of neuroimaging studies in high-grade gliomas

Case

A 62-year-old right-handed man with a history of hypertension and type 2 diabetes mellitus presents to the emergency department after 3 days of progressive right arm weakness accompanied by speech problems and mild headaches. His wife reports he has also had problems with attention and memory over the previous 8 weeks. On examination, he has 4/5 weakness involving the right arm and 2/5 weakness of the right hand, as well as a mild motor aphasia. No sensory deficits are detected. The patient has no fever, cough, weight loss, hemoptysis, or gastrointestinal bleeding. There is no history of foreign travel, alcohol or drug addiction, or high-risk sexual behavior. Complete blood count, routine blood chemistry, and chest x-ray are normal. However, a CT scan of the head shows a single contrast-enhancing left frontoparietal lesion surrounded by low-density signal compatible with vasogenic edema.
1. Which of the following is the most appropriate and efficient approach to achieve a diagnosis with minimum delay?

A. assess results of blood cultures, sputum cytology and CSF analysis if the patient does not have significant midline shift
B. obtain a brain MRI with and without contrast, complemented with other sequences (spectroscopy, diffusion-weighted sequences, apparent diffusion coefficient maps, and perfusion parameters such as relative cerebral blood volume)
C. obtain a chest, abdomen, and pelvis CT scan and upper and lower gastrointestinal endoscopy
D. obtain a repeat CT of the brain with contrast in 4 weeks to assess for change in the size of the lesion
E. obtain brain and whole-body positron emission tomography (PET) scans

The preferred response is B (obtain a brain MRI with and without contrast, complemented with other sequences [spectroscopy, diffusion-weighted sequences, apparent diffusion coefficient maps, and perfusion parameters such as relative cerebral blood volume]). Patients with progressive mass lesions have a wide differential diagnosis. These range from pyogenic abscess and other CNS infections (e.g., toxoplasmosis, tuberculosis, cysticercosis, syphilis, fungal infection), autoimmune disorders (e.g., acute demyelinating lesions, sarcoidosis, Behcet disease), and subacute ischemic strokes to neoplastic lesions (brain metastases or primary brain tumors including gliomas and primary CNS lymphoma).

However, a prompt diagnosis is required to avoid neurologic deterioration. This is especially relevant when brain tumors are suspected because the patient’s clinical status is a strong prognostic factor for survival, and it also influences treatment options.

A thorough history, physical examination, and minimal workup can provide important clues on the nature of the lesion, especially when the diagnosis of brain tumor is being considered. Although MRIs do not have 100% specificity and sensitivity, they demonstrate the full extent of the lesion and may provide information suggesting a neoplastic lesion. Such information includes increased relative cerebral blood volume (rCBV) on perfusion imaging and characteristic increased choline-to-creatine ratios (suggestive of increased membrane turnover) and decreased N-acetyl aspartate (NAA), a marker of neuronal tissue, on magnetic resonance spectroscopy. These radiologic findings, used in conjunction with clinical judgment, usually provide sufficient diagnostic accuracy in cases of malignant brain tumors and allow surgery to proceed, avoiding delays in the diagnosis.

Only when MRI results are not clear regarding the likely neoplastic nature of the lesion are other complementary examinations necessary.

Brain MRI shows an isolated ring-enhancing lesion in the left frontoparietal lobe, surrounded by increased fluid-attenuated inversion recovery (FLAIR) signal, sparing the cortex, and involving the pyramidal pathways and opercular area. There is no midline shift; moreover, the enhancing and nonenhancing lesion shows an increased rCBV and hypointense signal in diffusion-weighted imaging (DWI) sequences with increased apparent diffusion coefficient (ADC) maps, together with detection of lactate and lipid peaks and an increased choline-to-creatine ratio and decreased NAA on magnetic resonance spectroscopy, suggesting that a high-grade glioma is the most likely diagnosis.

2. Which is the best initial medical treatment for this patient at this time?
   A. 4 mg to 8 mg dexamethasone daily, given in one or two daily doses
   B. 4 mg to 8 mg dexamethasone daily, given in three to four daily doses
   C. 12 mg to 16 mg dexamethasone daily, given in one or two daily doses
   D. 12 mg to 16 mg dexamethasone daily, given in three to four daily doses
   E. 500 mg acetaminophen every 8 hours, avoiding steroids

   The preferred response is A (4 mg to 8 mg dexamethasone daily, given in one or two daily doses). Glucocorticoids, by only partially understood mechanisms, decrease tumor-associated edema and reduce the vascular permeability of tumors. This effect commonly results in an improvement in the patient’s condition within 24 to 72 hours after the initiation of therapy. The benefits are usually transient and tend to benefit recent deficits more than the longer-established ones. Surgery in patients with extensive brain edema is associated with increased morbidity as a result of intraoperative increases in intracranial pressure and postoperative edema. Dexamethasone, which was initially investigated by Galicich and colleagues in 1961 for peritumoral edema, remains the most commonly used corticosteroid because of its lower mineralocorticoid effects compared with other corticosteroids. The general recommended starting dose (although based on few trials with small sample sizes) is 4 mg to 8 mg per day in patients with mild symptoms (as in this patient) and higher doses, such as 12 mg to 16 mg per day, in patients reporting more severe symptoms related to mass effect. Asymptomatic patients do not need to be started on corticosteroids. In general, because of its long half-life of 36 to 54 hours, dexamethasone can be administered as once-daily dosing in the morning, although it is commonly given at least twice daily. When primary CNS lymphoma cannot be ruled out by MRI, unless significant or life-threatening mass effect is present, corticosteroids should be avoided until a biopsy is performed to obtain a histologic diagnosis, as corticosteroids have a cytolytic effect that may prevent a diagnostic biopsy from being obtained.

The patient shows marked clinical improvement after 3 days of corticosteroid treatment at a total dose of 8 mg daily in two divided doses. His headaches have resolved, and there is partial recovery of speech and strength in his arm, although he still has some cognitive complaints and 3/5 weakness of his right hand.

3. Which of the following represents the next appropriate diagnostic and treatment step?
   A. administer chemotherapy or radiation therapy without histologic confirmation
   B. maintain the steroid schedule and refer the patient to the palliative care service because of the poor prognosis of his disease
   C. perform gross total resection despite the possibility of producing neurologic deficits following a radical removal
   D. perform maximal safe surgical resection assisted by preoperative functional MRI (fMRI) and, if necessary, intraoperative language and motor mapping techniques
   E. perform stereotactic biopsy because the tumor probably infiltrates eloquent areas

The preferred response is D (perform maximal safe surgical resection assisted by preoperative functional MRI [fMRI] and, if necessary, intraoperative language and motor mapping techniques). Although the prognosis in glioblastoma patients remains poor, treatments may increase overall survival and maintain the quality of life of patients, especially in those belonging to Radiation Therapy Oncology Group (RTOG) recursive partitioning analysis classes III to V. This prognostic classification is based on age, performance status, mental status, and extent of surgery. Although glioblastomas are characterized by their infiltrative nature, making curative resection impossible, these variables have been found to be important independent prognostic factors in most clinical series. It is also crucial at surgery to obtain enough tissue for an accurate definitive diagnosis and, increasingly, to provide material for molecular testing and eligibility for clinical trials. However, no class I evidence indicates that greater extent of resection leads to better overall survival, and randomized trials addressing this question may never occur. One phase 3 trial assessed the value of resection guided by 5-aminolevulinic acid, a precursor in the hemoglobin synthesis pathway that elicits the synthesis and accumulation of fluorescent protoporphyrin IX within glioma cells and, under blue-violet light, permits direct visualization of tumor tissue during the operative session. The study demonstrated that patients with gross total resection had significant improvement in 6-month progression-free survival. Retrospective studies suggest that the benefit of surgery is greatest when more than 95% of the tumor can be removed, but some survival benefit may exist with resections as low as 78%. To date, general consensus favors maximal safe resection. Although the resection must be balanced by the risk of neurologic compromise, advances in fMRI and intraoperative motor and language mapping enable resection of tumors located in eloquent brain areas with minimal morbidity, as demonstrated in a meta-analysis that included 8091 patients with supratentorial gliomas.


The patient undergoes fMRI, which shows that the tumor is adjacent to the language area, leading to surgery with intraoperative neurophysiologic monitoring with language and motor mapping. The immediate postsurgical MRI shows a 95% tumor removal from its initial volume, and he has no new neurologic symptoms postoperatively. After the postoperative recovery, the patient has a Karnofsky Performance Status Scale score of 70. The pathology report indicates that the tumor is a glioblastoma (World Health Organization [WHO] grade IV). Following surgery, the patient’s corticosteroid dose is tapered to 4 mg dexamethasone daily. He is referred to the neuro-oncology clinic for additional treatment options.

4. Which of the following is the most appropriate next step in medical management of this patient?

A. progressive tapering of corticosteroids until the patient is off them completely if no worsening of neurologic symptoms occurs
B. prophylactic use of lacosamide to reduce the risk of seizures and progressive tapering of corticosteroids until the patient is off them completely if no worsening of neurologic symptoms occurs
C. prophylactic use of levetiracetam to reduce the risk of seizures and progressive tapering of corticosteroids until the patient is off them completely if no worsening of neurologic symptoms occurs
D. prophylactic use of phenytoin to reduce the risk of seizures and progressive tapering of corticosteroids until the patient is off them completely if no worsening of neurologic symptoms occurs
E. prophylactic use of valproic acid to reduce the risk of seizures and progressive tapering of corticosteroids until the patient is off them completely if no worsening of neurologic symptoms occurs

The preferred response is **A (progressive tapering of corticosteroids until the patient is off them completely if no worsening of neurologic symptoms occurs)**. Corticosteroids should be tapered off as soon as possible to avoid complications. In addition to the known complications of long-term corticosteroid use, evidence also exists that these medications reduce the effectiveness of subsequent antitumor therapy. Prophylactic antiepileptic drugs (AEDs) are not needed in patients with brain tumors who have not had seizures. Approximately 30% of patients with high-grade gliomas present with seizures, and another 20% to 30% will develop seizures sometime during the course of their illness. The risk of seizures is lower in patients with brain metastases. Approximately 20% of metastatic patients present with seizures and another 10% to 20% will develop seizures during the course of their illness. The pathogenesis of tumor-related seizures is not completely understood and is likely to be multifactorial, involving genetic alterations of proteins, ion channels, and receptors, and dependent upon specific tumor cell type and localization.
Emerging evidence shows that the increased risk of seizures in tumors is related to downregulation of the excitatory amino acid transporter 2 (EAAT-2) and upregulation of the cysteine exo- (or anti-) transporter (Xc[-] transporter), resulting in increased concentrations of extracellular glutamate. The increased risk of seizures can be reduced in preclinical models using the Xc(-) transporter–blocking agent sulfasalazine. Currently, no evidence shows that prophylactic AEDs are useful; if they are given perioperatively, they should be tapered and discontinued after the first postoperative week. These recommendations were proposed in a practice parameter from the American Academy of Neurology in 2000. This practice parameter, which also included a meta-analysis of the available prophylactic studies of AEDs in patients with brain tumors, concluded that seizure prophylaxis was not effective in preventing first seizures in patients with brain tumors who had no history of epilepsy and that the incidence and severity of adverse events related to AEDs were appreciably higher in patients with brain tumors than in the general population of patients receiving anticonvulsants. Two additional meta-analyses have subsequently been performed over the past 10 years showing similar findings, although one considers the evidence as inconclusive at best. Moreover, the latter study noted that the increased risk of adverse events reported in patients with brain tumors receiving AED therapy were obtained from retrospective studies, making it possible that this was overestimated. However, only older AEDs, such as valproic acid, phenytoin, and phenobarbital, were used in the studies included in the meta-analyses; the value of newer AEDs with better side effect profiles remains to be tested. Meta-analyses of the studies evaluating AEDs for prophylaxis following craniotomies for any reason, and for brain tumors, found no benefit of prophylaxis after the first postoperative week.


The patient is decreased to 4 mg of dexamethasone after the first postoperative week. On his postoperative evaluation, the patient is doing well with the same Karnofsky Performance Status Scale score and neurologic function as the immediate presurgical evaluation. In addition to a histologic diagnosis of glioblastoma, additional molecular analysis of the tumor shows the promoter of the O-6-methylguanine-DNA methyltransferase (MGMT) gene is methylated, the isocitrate dehydrogenase 1 (IDH1) gene is not mutated, the epidermal growth factor receptor (EGFR) is amplified, and Ki-67 index (a cellular proliferation marker) is 38%. 

5. What is the most appropriate oncologic treatment for this patient?

A. a clinical trial that includes radiation therapy plus concurrent and adjuvant temozolomide as well as assessment of an investigational drug
B. radiation therapy
C. radiation therapy with concurrent temozolomide, followed by temozolomide
D. radiation therapy with concurrent temozolomide plus bevacizumab, followed by temozolomide and bevacizumab
E. surgery only

The preferred response is A (a clinical trial that includes radiation therapy plus concurrent and adjuvant temozolomide as well as assessment of an investigational drug). Surgery alone only increases survival by a few months in most patients with glioblastoma (median 3.2 months). The standard management for these patients includes maximal safe resection, followed by fractionated radiation therapy (total dose of 60 Gy in daily fractions of 1.8 Gy or 2 Gy) with concurrent temozolomide (an oral alkylating agent) chemotherapy, followed by an additional 6 months of adjuvant temozolomide. The addition of temozolomide results in a significant survival benefit with modest additional toxicity compared to radiation therapy alone. However, even with meticulous surgery and strict chemotherapy compliance, recurrence is inevitable. The overall prognosis remains poor, with a median overall survival rate of 14.6 months and 5-year survival rate of 9.8% in patients treated with radiation therapy and temozolomide. For this reason, the National Comprehensive Cancer Network recommends participation in a clinical trial to improve the results obtained with the current standard treatment (radiation therapy plus concomitant and adjuvant temozolomide) as the best management of patients with glioblastoma. Unfortunately, two recent phase 3 trials using bevacizumab (a monoclonal antibody against vascular endothelial growth factor [VEGF]) in addition to standard combined chemotherapy and radiation in newly diagnosed glioblastoma patients failed to show a benefit over standard treatment.

6. What is the most appropriate next step in this patient’s management?

A. obtain brain MRI before starting adjuvant treatment, then go on with the planned treatment irrespective of the status of the irradiated lesion

B. obtain brain MRI before starting adjuvant treatment, then go on with the planned treatment unless a new lesion is clearly visible outside the radiation field

C. obtain brain MRI to assess the response, and if the residual tumor is larger than on the postsurgical MRI, assume that it is due to early progression of the disease and change the treatment

D. obtain brain MRI to assess the response, and if the residual tumor is larger than on the postsurgical MRI, obtain a new biopsy

E. proceed with the adjuvant temozolomide, and obtain brain MRI to assess the response after two or three temozolomide cycles

The preferred response is B (obtain brain MRI before starting adjuvant treatment, then go on with the planned treatment unless a new lesion is clearly visible outside the radiation field). MRI of high-grade gliomas during and after radiation therapy, especially if the patient has also been treated with temozolomide, can show increased contrast enhancement due to transiently increased permeability of the tumor vasculature or to an inflammatory process from radiation or combined chemotherapy and radiation. This phenomenon, termed “pseudoprogression,” can be observed in 10% to 30% of patients and may be more frequent in patients with a methylated MGMT gene promoter. Therefore, it is difficult to reliably assess response using MRI performed during this time frame. To address this problem, the Response Assessment in Neuro-Oncology (RANO) Working Group proposed new neuroimaging response criteria. Given the difficulty of differentiating pseudoprogression from true progression in the first 12 weeks after radiation, the first scan performed about 4 weeks after radiation should be considered as the new baseline for all further follow-ups, unless the enhanced lesion appears clearly outside the radiation field. Therefore, although an MRI is usually performed before starting adjuvant temozolomide treatment, the patient can continue with therapy even if the scan shows more enhancement as long as no new lesions are found outside of the main radiation field. If the patient is very symptomatic, surgical resection is occasionally recommended to reduce mass effect and obtain a more definitive diagnosis of recurrent tumor or pseudoprogression. However, even with surgery, the diagnosis is not always conclusive.


In addition to repeating the brain MRI, which of the following drugs is most appropriate for the initial management of this patient’s seizure?

A. lacosamide  
B. lamotrigine  
C. levetiracetam  
D. oxcarbazepine  
E. phenytoin

The preferred response is **C (levetiracetam)**. The efficacy of older and newer AEDs on tumor-related seizures have not been compared. Therefore, to date, no firm evidence-based guidelines exist regarding the optimal AEDs for management of seizures in these patients. However, some practical considerations can be taken into account when selecting a first-line AED:

1. A drug that has an IV preparation can be useful, especially in the perioperative period or when the patient cannot take medications by mouth.
2. The AED selected must achieve therapeutic concentrations relatively quickly.
3. Second- and third-generation AEDs have not proven to be more effective than older AEDs, although they are generally better tolerated.
4. Among AEDs, levetiracetam and valproate have been the most widely used in treating glioma-related seizures. They are both effective and generally well tolerated, alone or in combination.
5. Levetiracetam and valproic acid have no significant effects on the metabolism of the commonly used antineoplastic agents, such as temozolomide and bevacizumab. Valproic acid is associated with increased hematologic toxicity when used with temozolomide, but this toxicity usually does not result in a significant reduction in the number of cycles or the total dose of chemotherapy administered to the patients.
6. Some retrospective data and a meta-analysis study show that treating patients with glioblastomas with some first-generation AEDs, such as valproic acid, is associated with improved survival.²,³,⁴ Although this has not been
confirmed by prospective trials and the underlying mechanism remains uncertain, valproic acid is often recommended as first-line AED therapy in Europe.\(^4\) In the United States, levetiracetam is generally recommended as first-line therapy because of its ease of use and rapid onset of action. Second-line AEDs may include lacosamide, valproic acid, lamotrigine, and pregabalin, among others. In patients with new seizures, an MRI is usually advisable to rule out spontaneous intratumoral bleeding or tumor progression, which present with seizures in 19% of patients.\(^1\)


Levetiracetam is started. A repeat brain MRI does not show tumor-related complications or tumor progression. The patient continues with his chemotherapy treatment as planned. At the end of the sixth adjuvant temozolomide cycle, a new MRI shows significant reduction of the T1 gadolinium-enhancing lesion. However, clinically the patient has deteriorated. While hand strength and language are slightly improved, he has serious difficulties getting up from a chair, walking, and climbing stairs, as well as new-onset bilateral tremor in both hands. He is irritable and has insomnia and blurred vision.

8. How should this patient’s new neurologic problems be managed?
   A. give benzodiazepines
   B. increase dexamethasone dose to 8 mg daily
   C. obtain nerve conduction studies
   D. obtain spinal cord MRI to exclude drop metastases or leptomeningeal dissemination
   E. withdraw dexamethasone progressively and completely

The preferred response is E (withdraw dexamethasone progressively and completely). Treatment with corticosteroids is commonly associated with considerable undesirable effects. These complications can be observed after taking the medications for weeks or months. Their severity corresponds to the dose, duration of therapy, low serum albumin levels (high risk with albumin levels less than 2.5 g/dL), and the potency of the medication chosen. Proximal myopathy (especially with the fluorinated steroids), behavioral changes, visual blurring, tremor, insomnia, and reduced taste and smell are the most common neurologic side effects of corticosteroids. In addition, patients may experience well-known complications, such as cushingoid features, diabetes mellitus, and osteoporosis. Fortunately, most of these complications resolve after steroid withdrawal, although the recovery from some complications, such as myopathy, can take several months.\(^1,2\) Therefore, it is important to always try to taper patients off corticosteroids; maintaining them on a constant dose...
indefinitely will inevitably lead to complications. However, no evidence-based guidelines exist for the tapering of dexamethasone in patients with brain tumors. In most studies, the steroid dose is reduced by 25% to 50% every 4 to 5 days for patients showing improvement of neurologic symptoms. In patients with progressive or persistent tumors who worsen with dose reduction, prolonged steroid use may be warranted, and careful monitoring for adverse events has to be implemented. Occasionally, bevacizumab may be used for its steroid-sparing effects. It is also important to encourage patients to exercise to attempt to avoid a steroid myopathy. In patients with neurologic deficits that do not respond to corticosteroids, maintaining the medication is unhelpful and should be avoided. It is important to check that other medications taken by the patient are not contributing to potential side effects. For example, valproic acid can cause tremors, and levetiracetam can occasionally cause depression and irritability.


9. Which of the following next steps in management or diagnosis is most appropriate at this time?
   A. administration of an antidepressant
   B. administration of donepezil 10 mg/d
   C. administration of memantine 20 mg/d
   D. administration of methylphenidate 20 mg/d
   E. neuropsychological testing, including assessment for depression, and cognitive rehabilitation

The preferred response is E (neuropsychological testing, including assessment for depression, and cognitive rehabilitation). Cognitive impairment is one of the most prevalent symptoms in patients with brain tumors. It can be caused by multiple factors, including the direct effects of the tumor or as a result of treatment. Moreover, mood disorders or concurrent infections can precipitate or aggravate these deficits. Among all of these factors, radiation therapy is the main treatment-related factor causing cognitive impairment and even dementia. Several medical interventions have been evaluated to reduce or minimize the impact of radiation-induced cognitive impairment. Memantine, an N-methyl-D-aspartate (NMDA) receptor antagonist, was evaluated in a placebo-controlled trial in patients with brain metastases who received whole-brain radiation therapy. The medication, which was administered during radiation therapy and for the first 24 weeks afterward, was well-tolerated and delayed time to cognitive decline, with improvements in memory and executive functions. However, the trial failed to improve the
primary end point (verbal memory), and the results of several cognitive tests were not maintained during follow-up, although the large number of patients who dropped out of the study as a result of death undoubtedly contributed to these negative results.\(^1\) Moreover, since the drug was administered at the initiation of radiation therapy, its use after cognitive impairment has developed remains uncertain. Methylphenidate has been widely studied in childhood cancer survivors and has shown efficacy in improving attention and executive function with a good safety profile.\(^2\) However, its use in patients with brain tumors has not been evaluated in large controlled randomized studies. On the other hand, cognitive rehabilitation in a controlled randomized trial on patients with low-grade and high-grade brain tumors showed improvement in attention, verbal memory, and mental fatigue.\(^3\) In addition, a recently reported placebo-controlled phase 3 trial with the acetylcholinesterase inhibitor donepezil at doses of 5 mg to 10 mg showed possible benefit in improving verbal and working memory, visual and psychomotor performance, and executive function in patients with severe baseline cognitive impairment.\(^4\) However, when patients with less-severe cognitive impairment were included, the primary end point (cognitive composite score) did not show significant differences compared to placebo.\(^4\) AEDs can have a negative impact on cognition, especially the \(\gamma\)-aminobutyric acid–mediated (GABA-ergic) AEDs, and should be administered as monotherapy and in the lowest effective doses whenever possible. However, a recent study suggested that the use of levetiracetam and valproate in patients with high-grade gliomas did not result in cognitive impairment and may even have had a beneficial result on verbal memory compared to patients not receiving AEDs.\(^5\)


Formal neuropsychological testing shows no evidence of depression. Cognitive rehabilitation is started. Over the following months, the patient’s MRIs show stable disease. However, he remains tired throughout the day and has no energy for many of his daily activities.
10. Which of the following is the most appropriate intervention to improve this patient's fatigue?

A. administration of erythropoietin 30,000 units weekly
B. administration of low doses of steroids
C. administration of methylphenidate 10 mg/d or modafinil 200 mg/d
D. administration of paroxetine 20 mg/d
E. switch from levetiracetam to gabapentin

The preferred response is C (administration of methylphenidate 10 mg/d or modafinil 200 mg/d). Cancer-related fatigue is one of the most common symptoms reported by patients with cancer, especially patients with brain tumors. The prevalence exceeds 60% and may be present at diagnosis, during treatment, or even well after active therapy has been completed. \(^1\) This fatigue negatively impacts the patient's quality of life. \(^1\) Before starting any medications for fatigue, it is important to exclude conditions that may contribute to fatigue, such as anemia, depression, metabolic disorders, and endocrine dysfunction, especially hypothyroidism or adrenal insufficiency. Therefore, blood tests, including complete blood count, thyroid function tests, and possibly morning cortisol and testosterone levels, should be performed. It is also important to consider treatment-related factors, such as chemotherapy, radiation therapy, and AEDs, as potential causes of the fatigue. In addition to a direct effect of radiation therapy in producing fatigue, radiation therapy can also cause progressive hypothalamic-pituitary axis insufficiency. At 5 years with total doses of 40 Gy of radiation, 50% of patients will have thyrotrpin deficiency. \(^2\) It is important not to miss this cause of fatigue as these patients will greatly benefit from thyroid replacement therapy. A recent meta-analysis about the efficacy of drug therapy for cancer-related fatigue management showed that methylphenidate at 10 mg or 20 mg is a safe and useful intervention. \(^3\) Modafinil 200 mg/d also appeared useful in a phase 3 trial. \(^4\) Antidepressants and hemopoietic growth factors have not been shown to be beneficial for fatigue and can even be unsafe, as in the case of erythropoietin. \(^3\) Because many patients are on long-term corticosteroids, occasionally fatigue may be caused by adrenal insufficiency as the corticosteroids are tapered. In these patients, resumption of a low dose of corticosteroids followed by a slow taper may be beneficial. Because dexamethasone has low mineralocorticoid activity, hydrocortisone or prednisone may be preferable in treating adrenal insufficiency. Other potential interventions include switching or reducing the AED dose. Drugs acting on the GABA-ergic system have the highest incidence of fatigue, followed by gabapentin and levetiracetam, which mainly inhibit sodium channels. \(^5\) Aerobic exercise has been shown to be beneficial for fatigue in other cancers and may potentially be effective for patients with brain tumors. \(^6\)

\(^4\) Jean-Pierre P, Morrow GR, Roscoe JA, et al. A phase 3 randomized, placebo-controlled, double-blind, clinical trial of the effect of modafinil on cancer-related fatigue among 631 patients...
blood tests, including assessment of endocrine function, are unrevealing. The patient’s fatigue improves slightly with administration of modafinil, and he remains clinically stable for the next 7 months. However, the patient then develops increased right arm weakness. An MRI shows a new enhancing lesion adjacent to the surgical cavity, which is not felt to be amendable to gross total resection.

11. Which of the following tumor treatments is the best option for this patient?
A. bevacizumab plus irinotecan
B. CCNU (lomustine) plus bevacizumab
C. dose-dense temozolomide schedule (75 mg/m
de 2 to 100 mg/m
de 2 for 21 consecutive days of a 28-day cycle)
D. enrollment in a clinical trial
E. temozolomide rechallenge

The preferred response is D (enrollment in a clinical trial). No standard treatment exists for recurrent glioblastoma. Surgery may occasionally have a role in relieving symptoms from mass effect and provide time for additional therapies to work, but it is unlikely to prolong survival significantly unless a gross total resection can be achieved. The value of repeat radiation is unclear. Treatment with chemotherapeutic agents such as CCNU and temozolomide have produced modest prolongation of 6-month progression-free survival but questionable improvement in overall survival. No evidence has shown that combination therapies are better than single agents. Rechallenge with temozolomide can be helpful in patients who did well initially with prior adjuvant temozolomide and a subsequent treatment-free period (6-month progression-free survival of approximately 35%) but tends to have minimal benefit in patients who progress while on standard-dose temozolomide. Dose-dense regimens do not appear to be more effective than standard dose regimens. The prognostic and predictive role of tumor MGMT methylation status in recurrent disease is controversial.

Another option is bevacizumab, a humanized monoclonal antibody against vascular endothelial growth factor (VEGF). This drug received accelerated approval by the US Food and Drug Administration (FDA) in 2009 for treatment of recurrent glioblastoma based on improvement in response rate and response duration relative to historical controls in two phase 2 trials (progression-free survival ranging from 4.2 to 5.6 months). However, it is unclear whether bevacizumab alone improves overall survival, and it is currently not approved in Europe for use in patients with glioblastomas. Recently, a randomized phase 2 trial showed that the combination of bevacizumab and CCNU in patients with recurrent glioblastoma appeared to have improved progression-free and 9-month survival compared to either agent alone. This led the European Organisation for Research and Treatment...
of Cancer (EORTC) to conduct a phase 3 trial evaluating the combination. Given the limited available options, the best choice for these patients is to consider enrollment in a trial evaluating a new treatment approach. Important progress has been made in targeted molecular therapies and immunotherapies that will, with hope, translate into improved patient outcomes as a result of clinical trials.


The patient does not have access to a clinical trial near his home, so he proceeds with treatment with CCNU and bevacizumab. He is stable neurologically, but his fatigue worsens. The third cycle of CCNU is delayed because of hematologic toxicity. MRI performed prior to initiation of the third cycle shows a significant reduction of the T1-weighted contrast-enhancing areas with increase in the extent of FLAIR signal.

12. What is the most accurate assessment, given this MRI result?

A. the patient had a partial response because the T1-weighted contrast-enhancing lesion has decreased in size
B. the patient has progressive disease because the FLAIR signal has increased
C. the patient has stable disease because he has not changed clinically
D. the patient has stable disease because the T1-enhancing lesion has decreased in size but the FLAIR signal has increased
E. this is a pseudoprogression phenomenon due to the nitrosourea treatment

The preferred response is **B (the patient has progressive disease because the FLAIR signal has increased).** Antiangiogenic therapies, such as bevacizumab, can reduce vascular permeability and decrease contrast enhancement within 1 to 2 days after initiation of therapy. These apparent responses, called pseudoresponses, may be partially the result of normalization of abnormally permeable vessels and are not necessarily indicative of a true antglioma effect.1–4 As a result, radiologic responses in studies with antiangiogenic agents should be interpreted with caution.5,6 Moreover, it is known that some patients who
initially experience reduction in tumor contrast enhancement subsequently develop progressive increase characterized by an increase in nonenhancing T2/FLAIR signal suggestive of infiltrative tumor. For this reason, the RANO Working Group proposed an updated response criteria, in which a significant increase in T2/FLAIR sequences compared with the baseline MRI or the best response achieved after initiation of therapy, in absence of alternative explanations such as radiation injury, ischemic or demyelinating events, infections, seizures, or postoperative changes, should be interpreted as progressive disease. On the other hand, pseudoprogression occurring more than 1 year after radiation therapy during second-line treatment with nitrosoureas is very uncommon.


Soon afterward, the patient's clinical condition begins to decline. After an extensive discussion of the goals of care, he decides to stop active therapy and focus on comfort measures.