ABSTRACT

The management of glioma has evolved considerably during the last decade as significant advances in surgery, cytotoxic chemotherapy, targeted biological therapy, and molecular tumor profiling have entered clinical practice. Gross total resection (GTR) has increasingly been used to treat patients with high-grade glioma, and recent clinical studies have documented improved quality of life and delayed time to glioma recurrence with this approach. Carmustine (BCNU) wafers may be considered for the treatment of focal tumors that are potentially treatable using GTR and that are not situated near critical functional brain areas. Newer biopsy techniques have made it possible to obtain tissue samples from brain regions that were previously inaccessible. In several clinical trials of temozolomide and radiation therapy, the DNA repair enzyme O6-methylguanine methyltransferase has emerged as an important predictor of disease course and response to therapy. Other biomarkers that have recently been evaluated in patients with glioma include proteins that are important in DNA repair and tumorigenesis, as well as newer magnetic resonance and positron emission tomography imaging techniques that provide information about tumor structure and metabolism. Recent clinical trials have continued to refine our understanding of the role of temozolomide, radiation therapy, inhibition of angiogenesis, and other approaches to the treatment of patients with glioma. Although glioma remains a challenging disease with a dismal long-term prognosis, recent advances provide encouragement for the continued development of new treatment options for these patients.


SURGICAL RESECTION FOR PATIENTS WITH NEWLY DIAGNOSED OR RECURRENT GLIOMA

A growing body of recent research has changed the way that many surgeons view the role of surgical resection for patients with newly diagnosed or recurrent glioma. During the last decade, gross total resection (GTR) has increasingly been selected for patients with high- and low-grade glioma, and promising new strategies have been developed that combine local therapy, chemotherapy, and radiation. New surgical techniques are also making it possible to obtain pathology samples from patients who have traditionally been considered inoperable, and the information provided by these techniques often has significant implications for patient management.

GROSS TOTAL RESECTION

Surgical resection has traditionally been considered...
an option for relatively few patients with high-grade glioma due to the poorly defined borders of these infiltrative lesions. More recently, GTR has increasingly been used for patients with high-grade glioma. GTR was historically defined by the surgeon on the basis of operating room observations. In contemporary clinical practice, GTR is defined by postoperative magnetic resonance imaging (MRI) findings, including the degree of contrast enhancement or remaining fluid-attenuated inversion recovery (FLAIR) signal abnormality. MRI assessment must be performed within the first 1 to 3 days after surgery to avoid confounding the interpretation of images by postoperative inflammation and disruption of the blood-brain barrier (BBB).

The role of GTR in the management of glioma is illustrated by the MRIs shown in Figure 1, which were obtained from 2 patients. The first patient presented with seizures and headache, and was initially diagnosed with an unresectable tumor due to its location within eloquent cerebral cortex. The patient underwent a successful total resection and implantation of 1,3-bis-(2-chloroethyl)-1-nitrosourea (carmustine or BCNU) wafers with no postoperative deficit, followed by radiation therapy and adjuvant temozolomide for 6 months. Treatment with an investigational inhibitor of the DNA repair protein poly (ADP-ribose) polymerase (PARP) is ongoing. The second patient presented with seizures, dysnomia, and headache, with MRI evidence of a lesion that involved cortical speech areas. The patient underwent a brain biopsy and was diagnosed with glioblastoma multiforme (GBM), which was initially classified as unresectable. GTR was performed without any postoperative deficits and followed by radiation therapy and temozolomide for 6 months. After a stable disease-free and steroid-free period of more than 16 months, the patient experienced a recurrence of GBM and underwent a second resection, with another recurrence 3 months later.

Gross total resection also has been used successfully in patients with poorly enhancing or nonenhancing lesions, and for patients who were initially treated with subtotal resection but who had significant residual impairment. Several recent reports have described significant benefits of cytoreductive surgery for patients with gliomas who do not have substantial postoperative neurologic deficits.

In addition to the potential benefits for patient quality of life, there is also evidence to suggest that surgical resection delays the time to glioma recurrence. In one recent study, investigators retrospectively examined clinical outcomes for up to 12 years in patients with low-grade glioma who underwent GTR, near-total resection (defined as <3 mm thin residual FLAIR signal abnormality around the rim of the resection cavity only), or subtotal resection (defined as residual nodular FLAIR signal abnormality). Patients who underwent GTR exhibited significantly longer overall survival ($P = .017$) and progression-free survival ($P = .043$) than patients in the other 2 groups, as well as a trend toward greater time to conversion to high-grade glioma ($P = .06$). The 5-year overall survival rates were 95%, 80%, and 70% for the GTR, near-total resection, and subtotal resection groups, respectively. A subsequent study examined outcomes for 1200 consecutive patients with high-grade gliomas who underwent GTR for either newly diagnosed disease or as a repeat resection. Patients who underwent GTR exhibited significantly longer survival for both primary resection and for repeat resection than patients who underwent near-total or subtotal resec-

![Figure 1. MRIs Illustrating the Role of GTR in the Management of Glioma](image-url)

**A.** This patient with seizures and headache underwent resection with BCNU wafers in April 2009, followed by radiotherapy and temozolomide for 6 months. The patient is currently receiving an investigational PARP inhibitor.

**B.** This patient with seizures, dysnomia, and headache underwent a brain biopsy and was diagnosed with GBM, which was initially classified as unresectable. GTR was performed without postoperative deficits, with radiation therapy and temozolomide for 6 months. After a stable disease-free and steroid-free period of more than 16 months, the patient experienced a recurrence of GBM and underwent a second resection, with another recurrence 3 months later.

BCNU = carmustine; GBM = glioblastoma multiforme; GTR = gross total resection; MRI = magnetic resonance imaging; PARP = protein poly (ADP-ribose) polymerase.

Images courtesy of Jaishri Blakeley, MD.
Gross total resection also has been associated with several other benefits. Patients are likely to require less steroid treatment, which reduces the risk of several steroid-related adverse events, including cushingoid habitus, steroid myopathy, peripheral edema, and hyperglycemia. By increasing the amount of tissue available for pathologic examination, GTR may help to improve diagnostic accuracy. GTR also may help to improve seizure control and make it possible to administer local therapies (eg, BCNU wafers), and is increasingly being required in clinical trials of new immunotherapy regimens.

**LOCAL THERAPY OF MALIGNANT GLIOMAS**

BCNU-loaded wafers were approved for the treatment of newly diagnosed malignant glioma in 2003 and for recurrent GBM in 1996. Implantation of BCNU wafers after tumor resection provides local delivery of a high concentration of cytotoxic therapy that is not limited by penetration of the agent through the BBB. BCNU wafers may be considered for the treatment of focal tumors that are potentially treatable using GTR and that are not situated near critical functional brain areas. The use of BCNU wafers has recently been a controversial topic among neurosurgeons because some studies have questioned the effectiveness of this approach. Central nervous system (CNS) infection and wound infection have been reported in some patients, with reported rates varying from 2% to as high as 28%. Some patients develop pronounced brain edema. In one study, 2 of 120 treated patients exhibited acute intracranial hypertension, which responded successfully to corticosteroid treatment in both cases. The incidence of radiation-related complications is similar to the rate observed with radiation therapy alone. Hence, there are side effects that may be associated with local BCNU wafers. However, there is substantial evidence from studies conducted in North America and in Europe that BCNU wafers can play an important role in the adjuvant treatment of patients with glioma. These randomized phase III studies have resulted in the US Food and Drug Administration (FDA) approval of BCNU wafers for both newly diagnosed high-grade malignant gliomas and recurrent GBM. Treatment is generally well tolerated and provides an alternative approach to multimodal therapy in patients who cannot tolerate systemic cytotoxic drugs.

As mentioned, BCNU wafers can serve as a safe platform for multimodality therapy. The effects of BCNU wafer implantation in combination with radiation therapy and temozolomide were examined in a retrospective review of 33 patients with newly diagnosed GBM. The median survival was 20.7 months, with a 2-year survival rate of 36%. The reported complications were rare and included site infection (1 case), perioperative seizures (2 cases), deep vein thrombosis (1 case), pulmonary embolism (3 cases), and cerebral edema requiring urgent management (1 case). BCNU wafers are also approved for recurrent GBM based on demonstrated improved survival of approximately 2 months in patients with recurrent GBM.
An example of the use of BCNU wafer implantation for recurrent disease is shown in Figure 2. This patient was a 48-year-old woman who was diagnosed with GBM in January 2005. After her initial resection, she received conformal radiation therapy and 12 months of treatment with temozolomide. She experienced significant temozolomide-related systemic complications, including *Pneumocystis carinii* pneumonia. In June 2006, she was diagnosed with recurrent GBM. She underwent resection with BCNU wafer placement and has remained recurrence-free since that time.

Ongoing clinical research continues to define the role of BCNU wafers in the treatment of GBM. A recent phase I dose escalation study examined the optimal dosing of BCNU wafers, with doses from 3.8% (62 mg) to as high as 28% (454 mg). The maximum tolerated dose was 20% BCNU by weight. Interestingly, this is roughly 5 times the dose currently available commercially. BCNU wafers have also been evaluated as a platform for combination therapy. For example, recent studies have examined the addition of O6-benzylguanine (O6-BG), which decreases the activity of the DNA repair enzyme O6-methylguanine methyltransferase (MGMT) and increases the efficacy of alkylating therapies such as temozolomide or radiotherapy. O6-BG has been associated with unacceptable toxicity when combined with systemic alkylating agents, but produced promising results in a recent study in which it was administered in combination with BCNU wafers.

Other advances in technology are also helping to improve outcomes in patients with GBM, including intraoperative MRI, functional imaging, and awake craniotomy. However, although advances in surgery and associated technologies can help to improve outcomes, they are also associated with important potential limitations. Surgery may result in significant vascular damage, both from removal of the tumor and from injury to traversing blood vessels to adjacent healthy tissue. In some cases, aggressive surgical treatment may cause ischemic events or other undesirable outcomes that can produce significant postoperative neurologic impairment and significantly decrease patient survival. For example, a recent study examined the impact of surgically acquired deficits on patient survival in 306 consecutive patients who underwent primary resection of GBM. Median survival was 12 months for patients with no new postoperative neurologic deficits, 9 months for those with new motor deficits (*P* < .05), and 9.6 months for those with new language deficits (*P* < .05). Thus, although aggressive surgical resection is desirable whenever feasible, maximal precaution is required to avoid postoperative deficits. It appears that improved surgical experience and developing techniques are permitting more aggressive resections without neurologic injury.

The “Inoperable” Patient: The Importance of Obtaining Pathologic Confirmation of the Diagnosis

It is usually possible to obtain a biopsy sample even when GBM is considered unresectable, and this sample may have a significant impact on the selection of a treatment strategy. This is illustrated by the case shown in Figure 3. This 58-year-old woman was previously diagnosed with demyelinating disease, and she presented with a new episode of confusion, headache, and vision changes. MRI revealed the large, inaccessible lesion shown in Figure 3. She was diagnosed with inoperable GBM and referred for hospice. The patient and her husband sought a second opinion, and a stereotactic biopsy revealed the lesion to be a primary CNS lymphoma. The patient was treated with 1 course of high-dose methotrexate, which resulted in significant shrinkage of the tumor. The lesion was no longer visible after 3 cycles of methotrexate.

This case illustrates that the development of technologies such as a frame-based and frameless stereotactic biopsy has made it possible to obtain biopsy samples even when GBM is considered unresectable.
specimens from very deep brain regions that were once considered inaccessible, including the brain stem. In addition, a transfrontal contralateral approach has been used to successfully biopsy, without significant morbidity, deep lesions of the brain stem and avoid the surface of the tentorium. Therefore, biopsy-guided therapy should be the standard regardless of whether the lesion is above or below the tentorium.

**SUMMARY: SURGICAL RESECTION FOR GLIOMA**

Recent research has prompted a significant change in the way that surgeons view GTR for the treatment of glioma. Historically, surgical resection was usually not considered an option for patients with advanced disease. More recently, several clinical studies have demonstrated that GTR should be considered the goal of surgical treatment of glioma when feasible. Postoperative neurologic symptoms have been associated with both diminished quality of life and increased risk of mortality, and GTR should therefore be performed when there is reasonable assurance of protecting against neurologic deficit. Regardless of the location of the tumor, pathology is important in selecting an appropriate treatment. Tissue diagnosis is required to ensure that an appropriate treatment plan is developed and applied. Newer surgical techniques have made it possible to obtain biopsy specimens from sites that would have been considered inaccessible in the past.

**THE USE OF MOLECULAR MARKERS AND BRAIN IMAGING TO PREDICT GLIOMA COURSE AND INDIVIDUALIZE THERAPY**

Temozolomide is the foundation of therapy for most patients with GBM. In the landmark randomized clinical trial of temozolomide given with radiation therapy and then in the adjuvant setting versus temozolomide alone for GBM, the median overall survival increased from 12.1 months with radiotherapy alone to 14.6 months with the combination of radiation and temozolomide (P < .001). Considerable recent research has examined several genetic, molecular, and neuroimaging markers that may identify tumors that are especially susceptible or resistant to temozolomide therapy.

**GENETIC MARKERS**

A large body of recent research has focused on the role of the DNA repair protein MGMT in modulating the susceptibility of cells to temozolomide. Temozolomide is an alkylating agent that targets N7 or O6 positions of guanine residues of DNA, resulting in interruption of cell division and subsequent cell death. MGMT and the closely related enzyme, O6-alkylguanine-DNA alkyltransferase, repair DNA damage by demethylating the O6 position of guanine. This returns guanine to its baseline state and allows cell division to continue. When the MGMT promoter is methylated, there is decreased MGMT transcription. Both the amount of MGMT and the methylation status of MGMT are important determinants of the cell's ability to repair DNA. Therefore, when MGMT is highly expressed or unmethylated, it is better able to counter the effects of temozolomide and other forms of alkylating therapy.

An analysis of data from the phase III trial of temozolomide with radiation therapy versus radiation therapy alone in patients with newly diagnosed GBM compared treatment outcomes for patients with or without...
MGMT promoter methylation.27 Across all patients, the suppression of MGMT by promoter methylation was a significant predictor of treatment outcome. The median overall survival was 18.2 months for patients with MGMT methylation versus 12.2 months for those with unmethylated MGMT (P < .001). The effect of adding temozolomide to radiation therapy was larger in patients with MGMT methylation than in those with unmethylated MGMT. In patients with MGMT promoter methylation, the median survival was 21.7 months with temozolomide and radiation versus 15.3 months with radiotherapy alone (P = .007). In patients without MGMT methylation, the median survival was 12.7 months with radiation and temozolomide versus 11.9 months for radiation alone (P = .06). Hence, MGMT promoter methylation is prognostic of a better outcome with radiation and temozolomide concomitant therapy.

Although MGMT expression and promoter methylation are important prognostic factors, there are potential limitations to the use of MGMT in treatment planning. MGMT testing is relatively complex, and there is no clear consensus on the optimal technique to evaluate MGMT activity. The polymerase chain reaction (PCR) procedure is widely considered the most sensitive and specific. However, the PCR technique requires cryopreserved tumor specimens to provide sufficient high-quality DNA. Immunocytochemistry has also been used to assess MGMT activity. Its advantage is that it is more widely available because it can be performed on fresh-frozen or paraffin-embedded tumor, and at lower cost. However, it may be influenced by extraneous factors such as fixation technique or glucocorticoid treatment and hence may be less reliable. In most recent clinical trials, investigators have attempted to routinely obtain fresh-frozen tissue that is suitable for DNA extraction in order to allow PCR-based MGMT analysis. It is typically quite difficult to obtain and correctly freeze tissue even in the setting of a highly structured clinical trial, and is probably more difficult in routine clinical practice. In addition, MGMT status testing is not yet routinely paid for by health insurance plans. Patients are therefore often required to bear the cost of this additional test (outside of the setting of a clinical trial). Given that thus far the results of this testing do not directly influence treatment recommendations, it is not clear if this testing should be part of the standard diagnostic evaluation of malignant gliomas. The correlation between test results and treatment outcome is not perfect, and there is considerable variability in the results due to factors such as the location of tissue sampled, the quality of the tissue, and how MGMT is assayed. Finally, the most effective treatment available currently for newly diagnosed malignant gliomas is temozolomide and radiation therapy both for patients with or without MGMT methylation. Until other treatment options are available that may make the stratification of patients based on MGMT status more clinically meaningful, it is not clear that this test should be performed clinically on a regular basis.

MGMT may also indirectly modulate other molecular and genetic markers that provide important prognostic information in patients with glioma. For example, recent in vitro studies have shown that methylation of the MGMT promoter is associated with overexpression of a mutant form of p53. This mutation increases tumor invasiveness and predicts a worse prognosis.28 Similarly, an inverse relationship between MGMT expression and activation of the tumor-suppressing protein phosphatase and tensin homolog (PTEN) has been described in preclinical models.29 In anaplastic oligodendroglioma, the most well-defined marker is the 1p/19q chromosome codeletion. Loss of heterozygosity at 1p and 19q is seen in both high- and low-grade oligodendroglioma, and predicts a better response to alkylating therapies.30,31 In vitro data and anecdotal patient observations have suggested that individuals with 1p/19q codeletions may also have a higher percentage of MGMT methylation.32 This may be one reason why these patients have better outcomes with treatment.

Mutations of the isocitrate dehydrogenase genes IDH1 and IDH2 have recently been identified as important prognostic factors in patients with glioma.33 This relationship was first identified in a genome-wide scan that was reported in 2008,34 in which IDH1 mutations were present in approximately 12% of all GBMs, but were present in every patient under the age of 30 with low-grade glioma. More recently, Yan et al found that patients with mutations of IDH1 or IDH2 tended to have better clinical outcomes than patients lacking these mutations.35 The protein that is encoded by this gene has not been identified, and the physiological function of the protein as well as its interactions with other molecular markers such as MGMT or PTEN are unknown. It appears that patients with IDH1 or IDH2 mutations generally do not bear mutations of other tumor-related proteins such as epider-
mal growth factor receptor, PTEN, or cyclin-dependent protein kinase, suggesting that this marker identifies an entirely distinct subset of patients with glioma. The clinical application of these mutations is not clear at present. It is possible IDH1 or IDH2 will help identify subtypes of patients with anaplastic astrocytoma or secondary GBM that have a lower likelihood of progression. Research is actively ongoing to determine the role of IDH1 and IDH2 and how they can best be applied clinically.

**IMAGING AS A PREDICTOR OF RESPONSE**

Magnetic resonance imaging is essential in the diagnosis and treatment of patients with glioma, yet it is an imperfect tool for evaluating tissue pathology. Gadolinium contrast is used to identify regions of BBB disruption but does not provide information about the specific cause of the disrupted BBB. Many other advanced imaging techniques have been proposed to predict who will respond to various treatments and distinguish treatment-related effects from tumor progression. Some of these techniques include magnetic resonance spectroscopy, apparent diffusion coefficient (ADC), amide proton transfer imaging, fluorodeoxyglucose positron emission tomography (PET), and new PET markers including $^{18}$F-fluoroethyl-tyrosine, $^{18}$F-fluorothymidine, and $^{18}$F-FDOPA. Recently, $^{11}$C-methionine has been used with conventional MRI and gadolinium contrast enhancement to predict treatment response to temozolomide. These investigators were able to use tumor amino acid metabolism at 3 months to identify patients with disease progression while on temozolomide. This is often very difficult to determine with standard MRI techniques. ADC has emerged as a potentially significant marker of treatment response in patients who are being treated with inhibitors of angiogenesis. ADC is routinely reported with MRI results, and provides a measure of overall cell density. ADC signal is low in areas where cells are densely packed (eg, in developing tumors), whereas high ADC levels indicate tissue necrosis. In one recent study, high ADC levels predicted better response to therapy with the anti-angiogenesis agent bevacizumab. A limitation of many of these imaging approaches is that they require technology that is available to very few research centers, are time consuming and expensive, and they have not been validated. Nonetheless, a critical limitation in the current practice of neuro-oncology is the accurate interpretation of tumor response. Hence, there are several ongoing studies to validate these developing imaging techniques in patients undergoing treatment for gliomas.

**DISCUSSION**

**Q:** Has there been any consideration of a clinical trial that offers the option of giving a patient something other than temozolomide for those with unmethylated MGMT?

**Dr Blakeley:** I would say that given the very good evidence that radiation and temozolomide prolongs survival for all patients with GBM regardless of MGMT status, I would not omit temozolomide and radiation from first-line treatment. I would consider adding an adjuvant therapy to temozolomide alone based on MGMT status, and it is possible that MGMT status at the time of recurrence would help you make decisions about an alkylation-based therapy versus some other strategy, such as immunotherapy. There are currently phase III trials that are assigning patients with newly diagnosed GBM to the experimental treatment arm based on MGMT status. However, the lack of alternative therapies that show promise of efficacy in the setting of unmethylated MGMT has limited this approach. It would be very reasonable to focus therapies for methylated versus unmethylated patients once we have additional treatment options.

**Q:** We describe MGMT as methylated or unmethylated. But within a particular patient, is MGMT methylation consistent across an entire tumor? Or does it vary from region to region?

**Dr Sills:** One study that examined this found a fairly homogeneous distribution of MGMT methylation within multiple sample points within high-grade gliomas. In one recent study, high ADC levels predicted better response to therapy with the anti-angiogenesis agent bevacizumab. A limitation of many of these imaging approaches is that they require technology that is available to very few research centers, are time consuming and expensive, and they have not been validated. Nonetheless, a critical limitation in the current practice of neuro-oncology is the accurate interpretation of tumor response. Hence, there are several ongoing studies to validate these developing imaging techniques in patients undergoing treatment for gliomas.

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Dr Olivi: I would also think time is going to play a factor. An enzyme is not at a constant level all of the time. There are going to be variations depending on the time of sampling, other pretreatment factors, history of steroids, and other agents that have been used in the patient's treatment.

**SUMMARY: BIOMARKERS IN THE MANAGEMENT OF GLIOMA**

Many potential genetic, molecular, and neuroimaging markers of prognosis or treatment response have been evaluated in patients with malignant gliomas. The DNA repair enzyme MGMT has consistently been shown to significantly influence disease course and the response to temozolomide and radiation therapy. MGMT also interacts with other tumor-related proteins that might serve as prognostic or predictive biomarkers. MRI techniques and nuclear medicine approaches are providing new methods to image physiological responses in addition to the anatomical changes standard imaging provides.

**EMERGING EVIDENCE FOR THE TREATMENT OF PATIENTS WITH MALIGNANT GLIOMA**

For patients with glioma, some treatment strategies are known to be effective and are supported by evidence from well-designed clinical trials, whereas other potential approaches remain investigational or speculative. As described earlier, maximal feasible resection is an important goal for patients with malignant glioma, and radiation with concurrent temozolomide is the current standard of care for patients with newly diagnosed GBM. This combination is also used in patients with anaplastic astrocytoma, although no clinical trials have clearly demonstrated the effectiveness of this strategy. It is even less clear whether this combination is appropriate for patients with anaplastic oligodendroglioma, particularly those with 1p19q codeletion. Several phase III studies will open this year to address these questions. Other commonly used therapies for GBM include BCNU wafers and recently, bevacizumab. BCNU wafers are FDA approved for recurrent GBM and can serve as an excellent platform for multimodality therapy in these patients. Bevacizumab monotherapy was recently approved by the FDA for recurrent GBM. Since its approval, bevacizumab has been widely used at the time of first recurrence for patients with GBM, although there are several limitations associated with bevacizumab that should be considered in a multispecialty setting to set forth the most rational strategy for each individual patient.

**TEMZOLOMIDE AND RADIATION THERAPY**

As described previously, the role of temozolomide in GBM is supported by the results of a large clinical trial that was initially reported in 2005 in the *New England Journal of Medicine*, in which the addition of temozolomide to radiotherapy was superior to radiotherapy alone in patients with newly diagnosed GBM. A recent report of 5-year outcomes from this study demonstrated significant long-term benefits of temozolomide and radiation versus radiation alone regardless of patient age, extent of resection, or MGMT methylation status. Overall survival after 5 years was 9.8% with temozolomide and radiotherapy versus 1.9% with radiotherapy alone ($P < .0001$). Although this survival rate is low, it represents a significant advance over previously available treatment strategies, and suggests that future efforts building on this initial success may provide even larger survival benefits. Although all patients benefited from temozolomide added to radiation therapy, the long-term report from this study showed that MGMT status was the single most predictive factor of a favorable response to temozolomide treatment.

The most common risks of combination therapy with temozolomide and radiation included hematologic adverse events such as thrombocytopenia and leukopenia. In a retrospective evaluation of hematologic toxicity associated with temozolomide and radiotherapy at a single institution, approximately 20% of patients experienced grade 3 to 4 thrombocytopenia, and 10% required platelet transfusions. The median duration of severe thrombocytopenia requiring transfusion was approximately 1 month, and 4% were transfusion dependent for 6 months or longer. Perhaps more importantly, 17% of patients in this study discontinued treatment due to thrombocytopenia. Discontinuation of treatment is especially significant for these patients because there are very few other options for tumor treatment if their hematologic function does not improve.

Changes in CD4+ cell count have also been increasingly recognized as an important factor in patients treated with temozolomide and radiation. All patients who are treated with this combination therapy exhibit some decline in CD4+ count, although the extent of this decrease varies from patient to patient.
Unpublished observations suggest that nearly all patients will experience a decline to less than 200/mm³ early in the course of combination therapy. This marks a profound loss of immune function that is similar to the definition of AIDS onset in patients with HIV infection. More importantly, the decline in CD4⁺ count appears to be sustained over time, and may be associated with decreased survival. However, it is unclear whether low CD4⁺ levels should lead to discontinuation of temozolomide, and if so, what the threshold CD4⁺ count for discontinuation should be.

**Other Clinical Considerations in Glioma Management**

Several other factors must also be considered in managing patients with glioma. Hyperglycemia is a common and potentially serious complication of glioma treatment. In a recent study, uncontrolled hyperglycemia (which was defined as blood glucose concentration >137 mg/dL) was associated with a lower survival rate in patients with glioma, even after controlling for steroid use, degree of resection, age, and performance status. Patient mobility is often impaired as a result of steroid-induced myopathy, especially for patients who require high steroid doses for long periods of time. Patients should be questioned about difficulty using stairs or when moving from a sitting to a standing position. Physical therapy is often helpful for patients with cancer who have significant mobility problems. Timely diagnosis and treatment of infection is essential, especially in consideration of the low CD4⁺ cell counts that are common among patients with glioma. Finally, seizure management is important to help maintain quality of life. Newer antiepileptic agents such as levetiracetam, zonisamide, and topiramate are often very effective and well tolerated, and are unlikely to interact with chemotherapy agents.

The term *pseudoprogression* has been used to describe a pattern of radiographic evidence of glioma progression immediately following treatment that is actually due to other causes, such as treatment-related inflammation, ischemia, infection, or seizures. Pseudoprogression occurs in as many as 20% of patients treated with temozolomide and radiation, and may account for as much as 50% of the post-treatment MRI change in these patients. For this reason, most clinical trials now require that patients continue MRI assessments for at least 3 months after the completion of treatment to ensure that progression is due to GBM rather than pseudoprogression. Although the identification of the underlying cause of pseudoprogression is clearly important in selecting an appropriate management strategy, it can be difficult to distinguish among the various potential causes of imaging changes using conventional imaging techniques. Clinical signs and symptoms (eg, worsening seizures or headaches) also do not reliably distinguish true progression from treatment-related MRI changes. For this reason, a great deal of work is ongoing to identify new imaging modalities that may better distinguish between tumor progression and pseudoprogression.

**Temozolomide and Radiation for Other High-Grade Gliomas**

The use of temozolomide and radiation therapy for other high-grade gliomas is illustrated by the patient shown in Figure 4. This 64-year-old woman presented with seizures, and MRI revealed the left temporal lobe brain lesion shown in Figure 4. She was treated with antiepileptic drugs and was stable with no new seizure episodes for 4 years. Four years after the beginning of treatment, a follow-up MRI revealed progression of the lesion. Because she was over 40 years old and had a large infiltrative high-grade glioma, she was not considered a candidate for complete resection. She underwent partial resection, and on the basis of tumor...
pathology was diagnosed with anaplastic astrocytoma. She began treatment with temozolomide and radiation therapy. At day 21 of combined therapy her platelet count decreased to 38,000 cells/µL; after 30 days, her white blood cell count was 90 cells/µL and her absolute neutrophil count was 0. She was hospitalized with neutropenic fever and began receiving platelet transfusions. She also was treated with antibiotic and antifungal therapy. After aggressive management of her infectious complications, she ultimately was able to be discharged to home. However, her platelet and white blood cell count never recovered to normal and she was not a candidate for systemic therapies when her tumor progressed several months later. Options were presented to the patient and her family; however, due to her poor functional status, they opted for supportive care alone.

Patients with anaplastic oligodendroglioma as defined as those with 1p19q codeletion are more likely to respond to any form of therapy (radiation therapy or alkylating chemotherapies). However, there is concern that radiation and temozolomide in these patients may increase the risk for brain injury, and there is no consensus about what therapy is optimal for newly diagnosed anaplastic oligodendroglioma with 1p19q codeletion. Ongoing clinical trials are examining several treatment scenarios, including radiation and temozolomide for anaplastic oligodendroglioma with or without 1p/19q, for low-grade glioma, and for anaplastic astrocytoma. This issue is of considerable clinical importance because clinical trials are increasingly examining agents that affect DNA repair enzymes in combination with other treatment strategies. For example, ongoing clinical trials of patients with MGMT methylation are examining PARP inhibition in combination with radiation and temozolomide. It is not known whether studies such as these pose a significant risk of CNS injury to the participants. Finally, it is not clear whether there are patient subgroups that are especially likely to benefit from temozolomide and radiation therapy.

**THE EMERGING ROLE OF ANGIOGENESIS INHIBITORS IN THE TREATMENT OF GLIOMA**

Treatments that target angiogenesis have been shown to produce several clinically significant effects in patients with glioma, including increased progression-free survival in patients with recurrent GBM, reduced dependency on steroids, and reduction of intracranial pressure for some patients. Published response rates have varied from approximately 20% to 57%, with lower rates in studies that used blinded central review. Even the lowest reported response rates compare favorably with published response rates of 8% to 10% in clinical trials of other treatment strategies for GBM. However, angiogenesis inhibition has not been shown to significantly improve overall survival. It should also be noted that progression in clinical trials is measured using gadolinium enhancement on MRI. It is therefore possible that the reported effects of anti-angiogenesis therapy actually reflect an effect on the BBB, rather than a specific antitumor effect.

There are also several potential limitations of anti-angiogenesis therapy. Inhibition of angiogenesis may change the natural history of GBM. For example, in an animal xenograft model study, tumors that were exposed to bevacizumab gained features of increased tumor invasiveness and migration. It is not clear to what extent this occurs in patients. It has also been suggested that inhibition of angiogenesis may cause a state of brain “addiction,” and that the withdrawal of bevacizumab in a responsive tumor may result in rapid tumor expansion. Recent data suggest that bevacizumab withdrawal probably does not promote explosive tumor growth, but that it may simply allow a tumor that has been progressing without mass effect due to edema and disrupted vasculature to become clinically apparent and symptomatic. Bevacizumab is also relatively expensive and has thus far not been shown to improve overall survival in patients with glioma. Bevacizumab is generally well tolerated and has side effects that do not overlap with the cytotoxic therapies it is often paired with. However, bevacizumab is associated with infrequent but potentially devastating adverse events, such as gastrointestinal perforation, intracranial hemorrhage, and thrombotic events (eg, deep vein thrombosis and pulmonary embolism). Several recent clinical trials have demonstrated that bevacizumab produces objective treatment responses in many patients with glioma. An open-label, multicenter, randomized phase II clinical trial examined bevacizumab as single-agent therapy or in combination with irinotecan in previously treated patients with GBM. Treatment response was examined using a blinded central review, and patients who progressed on bevacizumab alone were crossed over to combination therapy. Response to bevacizumab was noted for 28.2% of patients for bevacizumab alone.
versus 37.8% for bevacizumab plus irinotecan. The 6-month progression-free survival was 42.6% for bevacizumab alone and 50.3% for combination therapy. Adverse events included infection, fatigue, hypertension, headache, hemorrhage, and thrombosis. Patients on bevacizumab alone were less likely to have grade 3 or greater adverse events (46.4%) than patients treated with bevacizumab and irinotecan together (65.8%). A similar trial at the National Cancer Institute showed an objective response rate of 19.6% with a median duration of response of 3.9 months. Based on these reports, the FDA granted accelerated approval for single-agent bevacizumab for patients with progressive GBM. As a result of this approval, bevacizumab has been widely used in patients with recurrent or progressive malignant gliomas. However, some concerning trends are arising. For example, thus far there is no therapy identified to effectively control the tumor after progression on bevacizumab. Moreover, both clinical reports and preclinical reports raise the possibility that bevacizumab may possibly change the behavior of some tumors, perhaps actually increasing the propensity for infiltration.

Subsequent clinical trials have examined the efficacy of bevacizumab administration in patients with early or late glioma. In a pilot study, 10 patients with newly diagnosed GBM were treated with bevacizumab in combination with temozolomide and radiation therapy. Bevacizumab was administered at a dose of 10 mg/kg every 2 weeks, beginning of the first day of temozolomide and radiation therapy. The toxicity of this approach was generally acceptable. Adverse effects included presumed radiation-induced optic neuropathy, fatigue, myelotoxicity, wound breakdown, deep vein thrombosis, and pulmonary embolism. A larger phase II clinical trial to examine the efficacy and tolerability of bevacizumab for early GBM is in progress. Several other ongoing phase II and phase III trials are examining various bevacizumab strategies in early disease, including bevacizumab after radiation therapy and temozolomide, bevacizumab and erlotinib after radiation and temozolomide, and bevacizumab in combination with irinotecan.

Another recent phase II clinical trial examined the addition of bevacizumab to repeat radiation for patients with recurrent disease. Repeat radiation is often difficult for patients to tolerate and can result in extensive edema and the need for high steroid doses. In patients with focal lesions smaller than 3 cm, repeat radiation with bevacizumab produced an overall response rate of 50%, a 6-month progression-free survival rate of 65%, median overall survival of 12.5 months, and 1-year survival of 54%. Toxicities included intratumoral hemorrhage, wound dehiscence, and bowel perforation.

Use of bevacizumab in patients with GBM requires the consideration of several logistical issues. Anticoagulation is important because many patients with high-grade gliomas develop deep vein thrombosis. One recent study found that anticoagulation could be safely administered in patients receiving bevacizumab without increasing the risk of hemorrhage. A pre-existing symptomatic intracranial hemorrhage is an absolute contraindication to bevacizumab, and bevacizumab must be discontinued if symptomatic intracranial hemorrhage develops during therapy. However, for patients with evidence of a prior hemorrhage on MRI (eg, bleeding from a prior surgery), a recent retrospective study of 27 patients with recurrent malignant glioma found that it is reasonable to continue bevacizumab. Of 12 patients who had radiographic evidence of intracranial hemorrhage before treatment, only 1 patient required termination of therapy due to symptomatic progression of hemorrhage.

Some of the issues relating to bevacizumab therapy for patients with glioma are highlighted by the patient described in Figure 5. This 52-year-old man presented with aphasia and a seizure. MRI revealed the left posterior frontal lesion shown in Figure 5A. He underwent GTR followed by 3 cycles of radiotherapy and temozolomide. MRI revealed continued disease progression, and he was started on bevacizumab and irinotecan, which produced marked improvement in a follow-up MRI. After another 5 months, he began to develop progressive aphasia and hemiparesis, and his steroid requirement increased. He returned to surgery for debulking, which revealed extensive necrotic tissue. After surgery his speech improved but his motor function worsened. An MRI 3 months after his second surgery revealed improvement, but his function continued to decline. He elected to enter hospice, and died 2 months later. This case demonstrates that the use of bevacizumab may complicate the issue of when to perform surgery, and whether the safety of surgical therapy is changed by bevacizumab use. This case also points out that it is possible for the patient’s symptoms and MRI findings to diverge over time, with the scan improving but symptoms worsening.
DISCUSSION

Q: Is hyperglycemia something we can control? Or is it a function of the illness?

Dr Blakeley: I make robust efforts to control hyperglycemia. Of course there is a risk to that. If you overshoot then someone is hypoglycemic. So we have to be careful about how we manage it. I work closely with my referring physicians, primary care physicians, family practice doctors, and a diabetes clinic. It is very similar to the way in which we use an anticoagulation clinic for international normalized ratio.

Q: It has been suggested that MGMT methylation may indicate an increased likelihood of pseudoprogression. Is that useful?

Dr Blakeley: In a paper published last year, there was an association between pseudoprogression and MGMT status. The problem still remains of how to best assay it and what to say about what portion of the tumor or surrounding tissue was sampled. In many of these cases, the investigators have looked at the initial tumor at the time that the patient had the first resection, which might not be predictive of what is happening at the time of recurrence. That said, MGMT status may be an extra helpful piece of information to use when trying to assess if there is actual tumor progression versus pseudoprogression.

Dr Olivi: I think that probably this might be one expression of a particular individual predisposition to an increased susceptibility and subsequent development of pronounced treatment effects. I believe that one of the areas in which we can make progress is a relatively short period of time is the identification of patients who will be more prone to certain negative treatment reactions. There is an individual and non-uniform response to certain treatments that probably could be identified beforehand.

Dr Sills: I am much more likely to deem it pseudoprogression if there is a lack of new clinical symptoms. So my standard response would be if I have got a scan that looks progressive and I am concerned about pseudoprogression, if the patient is asymptomatic then I will usually opt for observation alone with shortening of the interval imaging period. Instead of waiting 8 weeks, I might bring them back in 4 weeks for another image. I have rarely seen a patient with true progression who remains asymptomatic for any great length of time. Thus the longer the patient goes without any new symptoms, the more I am inclined to believe it is pseudoprogression.

Q: In the last case you described, the patient's MRI appeared to improve while his symptoms worsened. What would you expect to see on FLAIR imaging in a case such as this?

Dr Sills: The patient's FLAIR imaging also improved at the time the patient was clinically deteriorating.

Dr Blakeley: That is a good point, because many times you will see the contrast enhancement getting better and better while the FLAIR and the diffusion will actually get worse. Sometimes that is interpreted as ischemia, but it might be caused by the concentration of cells, as we would expect with ADC.
Q: Could you comment on *P carinii* pneumonia prophylaxis?

*Dr Blakeley:* We use sulfamethoxazole and trimethoprim, which is administered Monday, Wednesday, and Friday at double strength and continued for the duration of therapy or until the CD4 count goes above 200. I measure CD4 count before therapy, 1 month after radiation and temozolomide, and monthly thereafter until I see it go above 200, and continue sulfamethoxazole and trimethoprim unless they have an adverse event. In that case, we would substitute something else, such as diaminodiphenyl sulfone.

Q: What is the pharmacokinetic profile of bevacizumab? When does it disappear from the system?

*Dr Blakeley:* Between 3 and 4 weeks.

**Summary: Emerging Evidence for the Treatment of Malignant Glioma**

During the last decade, progress in surgical techniques and chemotherapy has significantly improved the management of patients with glioma, with higher rates of durable response and better management of adverse treatment effects. Research has continued to highlight the importance of individualizing therapy and for the patient’s specific clinical features and overcoming practical obstacles to treatment, such as treatment-related leukopenia. Anti-angiogenesis therapy has emerged as an important option for many patients with glioma, although there are significant limitations and the optimal timing for initiating these agents is not known. A multidisciplinary approach is essential for planning and coordinating surgical care, chemotherapy, radiation therapy, and supportive care, and for evaluating and interpreting the response to treatment. Management of treatment and disease-related complications may have as great an impact on survival and quality of life as therapeutics and need careful attention. Recent advances in glioma therapy provide encouragement for the continued development of new treatment options for these patients.

**References**


mediates the combined deletions of 1p and 19q and predicts a better prognosis of patients with oligodendroglioma. Cancer Res. 2006;66:9852-9861.


