A 40-year-old male presents at the IU Simon Cancer Center with a two-week history of headaches, olfactory auras (abnormal chemical smells), and confusion. Routine laboratory studies performed to rule-out metabolic or infectious processes are negative. Magnetic resonance imaging (MRI) of the brain reveals a large right frontal enhancing mass suggestive of glioblastoma multiforme (GBM).

Of the estimated 22,000 new cases of primary brain cancer diagnosed annually in the United States, 80 percent are gliomas, and the majority of these are GBM, an aggressive malignancy that primarily affects adults. Preferentially located in the subcortical white matter of the cerebral hemispheres, GBM occasionally develops in the brainstem and spinal cord, and its etiology remains elusive. Most cases occur sporadically, and fewer than one percent are associated with recognized genetic syndromes (e.g., neurofibromatosis, Turcot syndrome, Li-Fraumeni syndrome).
The clinical history of de novo GBM* is short—generally less than three months. Headache is the most common presenting symptom, and it may accompany other indicators of increased intracranial pressure, such as nausea, vomiting, and seizures. Patients may also report a slowly progressive neurologic deficit (usually motor weakness), alterations in mental status, or changes in personality and mood.

“Imaging studies of the brain are essential to establish the diagnosis of GBM, and MRI with and without contrast is the study of choice,” says Stephanie Wagner, MD, clinical associate professor of medicine at the IU School of Medicine and co-director of the neuro-oncology program at the IU Simon Cancer Center. “These tumors characteristically have low-signal intensity on T1-weighted images and high-signal intensity on T2-weighted images and usually enhance with contrast.”

Enhanced T1-weighted images of GBM typically show a hypodense, necrotic central core circled by a dense ring of neoplastic cells with abnormal vessels (Figure 1). A broad surrounding zone of vasogenic edema containing invasive tumor cells is evident on T2-weighted or fluid-attenuated inversion recovery (FLAIR) images. Because of the infiltrative nature of these neoplasms, the area of enhancement does not represent the outer tumor border. Pathological studies show that gloma cells are easily identified within, and occasionally beyond, a two centimeter margin.

Positron emission tomography (PET) scans and MRI spectroscopy are generally not used to diagnose GBM but may be helpful for treatment monitoring (e.g., determining whether MRI changes result from radiation necrosis or a tumor recurrence). Cerebral angiograms are unnecessary for GBM diagnosis or clinical management.

The patient undergoes a craniotomy with a gross total resection of the tumor. Pathology is consistent with GBM World Health Organization (WHO) grade IV.

GBM is a highly infiltrating tumor and cannot be totally resected. Debunking surgery is performed when feasible to relieve neurological deficits related to mass effect and allow histologic diagnosis. Moreover, a number of studies have shown that gross or even subtotal resection confers a survival advantage over biopsy.

The current WHO classification of primary brain tumors lists GBM as a grade IV astrocytoma, one of three distinct types of brain gliomas (mixed cell types also occur). GBM is characterized by increased cellularity, nuclear atypia, and mitotic activity and contains areas of microvascular proliferation, necrosis, or both.*

Potential oncologic risk factors in patients with newly diagnosed GBM include age, performance status, and the presence of certain radiologic features, such as midline shift, perilesional edema, and cystic changes (concentric or eccentric). Increased concentrations of VEGF are also associated with GBM progression and decreased survival.

There are no clinical guidelines for routine use of angiographic procedures in newly diagnosed GBM, and the role of imaging in assessing response to therapy is still under investigation. While angiography has been useful in certain instances, such as in the detection of vascular malformations, it is not routinely performed in the management of GBM.

Figure 1. Preoperative MRI
A large, heterogeneous enhancing mass in the right frontal lobe suggestive of a high-grade glioma.

GBM, Bevacizumab (Avastin; Genentech, South San Francisco, CA) is the first new drug approved for GBM in more than a decade.

Angiogenesis and Bevacizumab
One of the hallmarks of cancer is sustained angiogenesis that allows a neoplasm to increase in size beyond a few millimeters. Vascular endothelial growth factor (VEGF) is an important mediator of tumor angiogenesis, in particular gliomas-induced angiogenesis.* GBM exhibits some of the highest concentrations of VEGF of any tumor type, and this over-expression correlates with high-grade malignancy and poor prognosis.

Postoperatively, the patient is treated with concurrent external beam radiotherapy and low-dose temozolomide. After three weeks, bevacizumab is added to the therapeutic regimen.

“Postoperative fractionated external beam radiotherapy and oral temozolomide are the current standard of care for patients with newly diagnosed GBM,” Dr. Wagner reports. “Although this combination of radiation and chemotherapy can prolong survival compared with radiotherapy alone, median survival is just 12 to 15 months, and less than 10 percent of patients are alive at five years.”

Once GBM progresses, few treatment options are available, and salvage chemotherapy regimens are usually unsuccessful. Among patients with recurrent GBM enrolled in phase II chemotherapy trials, the six-month progression-free survival rate was 15 percent, and median overall survival was 25 weeks.*

These grim statistics underscore the desperate need for new strategies to treat GBM. Bevacizumab (Avastin; Genentech, South San Francisco, CA) is the first new drug approved for GBM in more than a decade.

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Bevacizumab for Newly Diagnosed GBM
An antiangiogenic agent that is effective for recurrent disease usually achieves even greater benefit when used in patients with newly diagnosed cancer, prior to disease progression and the development of chemoresistance. Three phase II trials suggest this is true for bevacizumab, and two multicenter, randomized phase III trials are underway to confirm the benefits of adding bevacizumab to radiotherapy and temozolomide in patients with newly diagnosed GBM.

“Bevacizumab is a humanized monoclonal antibody inhibitor of VEGF and the first antiangiogenic therapy approved for use in cancer patients,” notes Dr. Wagner. “Bevacizumab has demonstrated antitumor activity in many solid tumors, including colorectal, breast, lung, and renal cell cancers, and the results of two phase II trials show it is also effective in patients with recurrent GBM.”

Bevacizumab was evaluated alone and in combination with irinotecan (CPT-11) in an open-label, multicenter, randomized trial that enrolled 167 patients with recurrent GBM. The majority of patients experienced tumor shrinkage during the treatment period, and six-month progression-free survival far exceeded the 15 percent rate for salvage chemotherapy. Specifically, patients in the bevacizumab monotherapy group had a six-month progression-free survival rate of 43 percent; this rate was 50 percent for those treated with both bevacizumab and irinotecan. The difference between the two groups was not statistically significant.

In a second study of 48 patients conducted at the National Cancer Institute, the six-month progression-free survival rate for bevacizumab monotherapy ranged from 18 to 48 percent, and six-month overall survival ranged from 44 to 75 percent.* Treatment was generally well tolerated in both trials.

“In 2009, on the basis of the results from these two pivotal studies, the US Food and Drug Administration (FDA) granted accelerated approval to bevacizumab for recurrent GBM,” says Dr. Wagner. “The findings from the phase II studies in untreated patients indicate that bevacizumab may enhance the effects of temozolomide by inhibiting chemotherapy-resistant cells,” points out Dr. Wagner. “And independent of any survival benefit, by tightening the blood-brain barrier and decreasing vasogenic edema, bevacizumab reduces neurologic signs and symptoms, such as headaches, seizures, and fatigue, thereby improving quality of life. Furthermore, the reduction in vascular permeability achieved by bevacizumab means that most patients can discontinue dexamethasone and avoid steroid-associated side effects. For all of these reasons, I now include bevacizumab upfront for virtually all of my patients with newly diagnosed GBM who are not enrolled in clinical trials.”
Following six weeks of daily radiotherapy, temozolomide, and bevacizumab, MRI scans of the patient’s brain show no evidence of disease. Treatment is halted for four weeks, after which another MRI is performed and shows the patient’s condition is stable. He is started on a regimen of temozolomide administered for five days every 28 days and intravenous bevacizumab 10 mg/kg given every two weeks. Brain MRI performed after 12 months of temozolomide and bevacizumab therapy shows a sustained remission (Figure 2). Both drugs are discontinued.

“The dramatic effects of bevacizumab on the MRI contrast signal result from the neutralization of VEGF-induced vascular permeability and stabilization of the blood-brain barrier,” explains Dr. Wagner. “This translates to decreased extravasation of gadolinium and intravascular fluid into the surrounding brain parenchyma, giving the appearance of tumor shrinkage.”

Despite the limitations of enhanced images, MRI demonstration of vascular permeability and gadolinium extravasation may be a useful biomarker of bevacizumab activity in situ. In one of the pivotal trials that led to FDA approval of bevacizumab for recurrent GBM, patients who did not have a partial response on early MRI scans had a significantly shorter progression-free survival.

The standard of care following concurrent radiotherapy and temozolomide is six months of temozolomide administered five days each month. Dr. Wagner says that most large centers, including the IU Simon Cancer Center, continue treatment for one year, at which time a repeat MRI and the patient’s functional status determine the next steps. Some patients elect to stop therapy altogether because their MRI is clean or they can no longer tolerate the toxicities of treatment. Some choose to continue with the same temozolomide-bevacizumab regimen, while others switch to once-monthly maintenance bevacizumab.

“MRI changes are often evident within 24 to 48 hours of the first bevacizumab dose(s),” Dr. Wagner continues. “Since this interval is too short for an actual anti-tumor effect, it means that decreased gadolinium enhancement is probably not an accurate marker of tumor mass in the setting of VEGF inhibition. Consequently, T2 and FLAIR imaging are needed to monitor GBM progression.”

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Figure 2. MRI after one year of temozolomide and bevacizumab therapy
Contrast-enhanced images at one year show stable changes or stable enhancement around the resection cavity. No changes around the resection cavity or other areas of the brain were noted throughout twelve months of therapy.

Figure 3. MRI at recurrence
Contrast-enhanced images show new enhancement around the posterior portion of the resection cavity and significant mass effect causing a right-to-left midline shift.

MRI of the brain obtained four months after the patient stopped treatment with temozolomide and bevacizumab shows new enhancement around the resection cavity (Figure 3). He reports increased olfactory auras despite use of an anti-epileptic medication as well as headaches and left facial droop. Both drugs are reinstituted at the previous schedule. MRI scans taken two months later show continued disease progression.
“Tumors can become resistant to the antiangiogenic effects of bevacizumab, and multiple pathways other than angiogenesis promote tumor growth,” she points out.

Figure 4. MRI after bevacizumab, irinotecan, and carboplatin

Contrast-enhanced images show a decrease in the amount of enhancement around the resection cavity and a decrease in mass effect.

“Tumors can become resistant to the antiangiogenic effects of bevacizumab, and multiple pathways other than angiogenesis promote tumor growth.”

Despite the efficacy of bevacizumab for recurrent GBM, the majority of patients do not achieve durable disease control. While there is some concern that bevacizumab may actually influence the pattern of disease progression and promote tumor invasion, many experts refute this notion, and Dr. Wagner concurs, providing an alternative explanation.

References

Future Directions for GBM Therapy

Although some patients with GBM survive long-term, this brain malignancy remains incurable, and the search continues to improve clinical outcomes. In the future, antiangiogenic therapies now in preclinical and clinical development, including cediranib, albendazole, and cilengitide, may be substituted for or combined with bevacizumab to enhance the tumorcidal effect. Targeted therapies are also being investigated, although Dr. Wagner is not overly optimistic about their potential.

“To date, targeted therapies have not been effective in GBM,” she comments. “Perhaps this is a dosing issue or results from drug administration after the disease recurs rather than at the time of diagnosis. But I suspect the main reason for the failures observed to date is that such treatment requires four to six weeks to take effect, and GBMs can double in size within a week to 10 days.”

More promising areas of research include vaccines to address the immune response seen in patients with GBM, molecular profiling to individualize treatment, and stem cell therapy, which capitalizes on the attraction of stem cells to primitive GBM cells.

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Dr. Wagner is certified by the American Board of Medical Oncology and is a member of the Society of Neuro-Oncology and the American Society of Clinical Oncology. She is the author of several scientific articles focusing on cancer research and treatment.