Treatment Advances for Glioblastoma: Tumor Markers and Targeted Treatments

June 01, 2007
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Although malignant brain tumors affect thousands of persons each year, treatment has not significantly advanced. For 3 decades, the standard of care was palliative surgery, radiation, and chemotherapy. Of these, radiotherapy was the only proven way to lengthen survival time. However, since 2005 the standard of treatment has changed thanks to studies showing positive results from daily temozolomide (Temodar) combined with radiotherapy.

Glioblastoma multiforme (GBM) is a devastating disease. Effective treatments are limited, and patient prognosis is poor. Most patients rapidly become debilitated. Median survival time is only 1 year.

Although malignant brain tumors affect thousands of persons each year, treatment has not significantly advanced. For 3 decades, the standard of care was palliative surgery, radiation, and chemotherapy. Of these, radiotherapy was the only proven way to lengthen survival time. However, since 2005 the standard of treatment has changed thanks to studies showing positive results from daily temozolomide (Temodar) combined with radiotherapy.

A phase 3 trial by Stupp and colleagues compared radiotherapy alone with radiation and concurrent daily temozolomide in patients with newly diagnosed GBM (both treatment groups received adjuvant temozolomide after completing the primary treatment regimen). Median survival for patients receiving radiotherapy plus temozolomide was 14.6 months compared with 12.1 months for patients receiving radiotherapy alone. This study, and another that looked at quality of life, showed that patients who received temozolomide in conjunction with radiotherapy had longer progression-free survival (PFS) and overall survival (OS) and had no decrease in quality of life compared with patients who received radiotherapy alone.

Response to temozolomide also might have a genetic basis. In conjunction with Stupp's work, Hegi and colleagues performed genetic testing showing that patients in whom the \(O^6\)-methylguanine-DNA methyltransferase (MGMT) DNA repair gene is silenced via a methylation promoter respond better to temozolomide than patients who do not have this genetic pattern.

PROGNOSTIC FACTORS
Survival rates since the 1980s have remained steady at 12 and 15 months. The 4 key prognostic factors include age, tumor grade, Karnofsky Performance Status, and the extent of tumor resection.

Age is the strongest prognostic indicator. Because advanced age is associated with loss of thymic CD8\(^+\) T cells, age-dependent decline in immune function may explain why age has such an important influence on patients with GBM.

HALLMARKS OF GBM
Hanahan and Weinberg outlined the 6 hallmarks of cancer: self-sufficiency in growth signals, evading apoptosis, insensitivity to anti-growth signals, sustained angiogenesis, limitless replicating potential, and tissue invasion with metastasis. Although researchers find these characteristics helpful for the laboratory investigation of cancer biology, they are not that useful to clinicians. However, these 6 laboratory-based cancer hallmarks can be reduced to 3 characteristics pertinent to clinicians: growth/proliferation, invasion, and angiogenesis, which are physiological characteristics of GBM and make this malignancy particularly deadly and resistant to treatment.

Growth/proliferation. The rapid growth of gliomas is probably caused by a cascade of activity at the genetic level originating from tyrosine kinases, such as epidermal growth factor and platelet-derived growth factor receptors; however, additional genetic alterations leading to uncontrolled proliferation are common. Drugs that inhibit these tyrosine kinases or their downstream targets could destroy GBM with minimal non-specific systemic toxicity.

Invasion. The aggressiveness of GBM also is characterized by the tumor's invasion into surrounding white matter. Although a sharply delineated enhancement of the tumor is seen on MRI, suggesting a discrete lesion, these masses often diffusely infiltrate the brain at the microscopic level.
The mechanism for this invasive process is unclear; but matrix metalloproteinases (MMPs)—either secreted MMP-2 and MMP-9 or membrane-bound MT1-MMP—may initiate extracellular matrix remodeling and cut a path for GBM cells. Furthermore, recent experimental data suggest that macrophages play an important role in tumor migration leading to tumor invasion and metastasis. In fact, soluble factors made by microglia can promote glioblastoma cell invasion, and this effect can be blocked by cyclosporin A. 

Angiogenesis. Angiogenesis is the third characteristic, which occurs in all tumors, including gliomas. During this process, endothelial cells from adjacent vasculature and circulating endothelial progenitors from bone marrow cooperate to create tumor microvessels. These tumor-induced microvessels have high permeability, permitting the leakage of gadolinium into the interstitial space during MRI. More important, the high permeability of these blood vessels leads to elevated interstitial pressure, which secondarily prevents adequate delivery of oxygen for radiotherapy to work and for chemotherapy to kill tumor cells.

TUMOR MARKERS

The diagnosis of GBM is still based on tumor histology, but emerging molecular diagnostics of key genetic and epigenetic changes is becoming an important part of GBM subclassification. Currently, the 2000 World Health Organization classification of tumors is widely used in clinical practice. It classifies astrocytic malignant gliomas into grade 3 anaplastic astrocytomas characterized by nuclear polymorphism and mitoses, and grade 4 GBM as having additional features of vascular proliferation and necrosis. Furthermore, advances in neuroimaging technologies, such as vascular MRI and 18-fluoro-39-deoxy-l-thymidine positron emission tomography (18F)FLT PET, have improved neuro-oncologists’ ability to measure tumor angiogenesis and metabolism. For identifying markers of tumor physiology, these functional neuroimaging tools are indispensable in the evaluation of targeted therapies. Although the current histological grading system has provided valuable prognostic information and is used in clinical trials, molecular genetics may offer a more precise subclassification of GBM. For example, O6 MGMT is a DNA repair protein that varies in different persons. The methylation status of the MGMT promoter is indicative of the transcriptional activity of the gene in tumor cells, and therefore is a measure of the DNA repair potential.

At the molecular level, treatment with temozolomide results in the formation of N7 and O6 methylguanine and O3 methyladenine DNA adducts. The MGMT gene encodes a DNA repair protein that removes alkyl groups from the O6 position of guanine (Figure). Thus, tumors with a high expression of MGMT are associated with resistance to treatment with alkylating agents. In contrast, the inactivation, or "silencing," of the MGMT gene by promoter methylation stops DNA repair and has been associated with prolonged survival in GBM patients. Furthermore, GBM could be further subclassified into primary and secondary GBM based on molecular features.

Primary GBM is a highly infiltrative tumor in elderly patients. Overexpression of epidermal growth factor receptor is common. In contrast, secondary GBM starts out as a low-grade glioma in young patients. It later transforms into GBM. The molecular changes are different and include overexpression of platelet-derived growth factor receptors at the initial stages and p53 mutations by the time tumors have become GBM.

Of note is that gene profiling can identify molecular subtypes of GBM that correlate more accurately with patient survival than with traditional histology-based classifications. Also, although tumors may be histologically identical to one another, their molecular differences can have a profound effect on treatment response.

Vascular MRI is an important tool for monitoring GBM. In identifying tumor markers, vascular MRI can provide important information on tumor microvessel physiology, providing parameters such as blood flow, permeability (often expressed as a constant Ktrans), diffusion, regional cerebral blood flow, mean transit time, and vessel diameter. These characteristics are indispensable for the evaluation of the effectiveness of antiangiogenic drugs and other targeted therapies.

For example, AZD2171 has been shown to decrease vascular permeability and support the concept of vascular normalization by pruning abnormal GBM vasculatures. The result is resolution of gadolinium enhancement and fluid-attenuated inversion recovery signals, suggesting decreased permeability and interstitial edema, respectively. Similarly, when bevacizumab (Avastin) was given to patients with radiation necrosis, a decrease in contrast enhancement was seen, suggesting an improvement in vascular permeability.

Metabolic imaging using 18F-fluorodeoxyglucose ([18F]FDG) PET has been problematic in the past because of the low signal-to-noise ratio (SNR). However, [18F]FLT PET has better sensitivity and specificity for primary brain tumors than [18F]FDG PET. The poor SNR in traditional [18F]FDG PET is
caused by high background $[^{18}F]$FDG signaling, because the normal brain also takes up a relatively large amount of glucose. But elevated levels of thymidine are only found in cells that are actively dividing. Because normal brain tissue has low proliferative potential, the increase in $[^{18}F]$FLT signaling would come primarily from dividing tumor cells. Currently, $[^{18}F]$FLT PET is an investigational procedure, but it holds promise for detecting the infiltrating edge of GBM, particularly in areas without blood-brain barrier breakdown. This type of functional tumor localization could aid in biopsy or surgical resection of GBM, as well as radiotherapy planning.

**NONSPECIFIC CYTOXIC CHEMOTHERAPIES**

Temozolomide is an orally administered cytotoxic agent that was approved by the FDA for the treatment of recurrent anaplastic astrocytoma in 1999, and for the treatment of newly diagnosed GBM in adult patients in 2005. This drug crosslinks the DNA of cancer cells so that they can no longer replicate. Temozolomide is quickly absorbed after oral intake. One third of it readily crosses into the blood-brain barrier. In addition to the conventional schedule of 5 days of temozolomide at 150 mg/m$^2$/d in 28-day cycles, clinical investigators have explored other dose- intensified schedules, including 7 days of temozolomide at 150 to 200 mg/m$^2$/d in 14-day cycles and 21 days of temozolomide at 75 mg/m$^2$/d in 28-day cycles. The dose-intensified schedules may be more effective than the conventional one but pose a risk of more opportunistic infections. However, a phase 3 study comparing various schedules of temozolomide for GBM is unavailable.

Other cytotoxic chemotherapy options for patients with GBM include irinotecan (Camptosar), combination procarbazine (Matulane), lomustine, and vincristine, or carmustine alone. The response rate is typically 15% or less. As a result, benchmark data derived from minimally effective traditional cytotoxic chemotherapies—such as 15% PFS at 6 months, 8% PFS at 1 year, 21% OS at 1 year, 6% complete response and partial response, and 33% complete response and partial response and stable disease—are typically used for comparison of new drugs for recurrent GBM in phase 2 trials.

**ANTIANGIOGENIC THERAPY**

Brem and colleagues first described the unique properties of tumor endothelium, consisting of microvessel proliferation, endothelial cell hyperplasia, and endothelial cell mitoses. Over the years, understanding these 3 major characteristics of tumor angiogenesis has aided the development of antiangiogenic therapies. First, microvessel density provides a quantitative measure of tumor angiogenesis. Second, low-dose daily non-tumoricidal chemotherapy, or metronomic chemotherapy, has been demonstrated to have an antiangiogenic effect in laboratory settings. Metronomic temozolomide also has shown antitumor activity in animal models where it reduced angiogenesis. Lastly, the recent demonstration that neuroblastoma cells with MYCN oncogene amplification incorporate into tumor microvessels suggests that there are mechanisms that lead to endothelial cell hyperplasia and limit the effectiveness of single-agent antiangiogenic treatment. Therefore, new therapies targeting both endothelial precursors and tumor-derived endothelial cells in the tumor microvessels may be necessary.

Emerging evidence suggests that antiangiogenic treatment may be effective for GBM, particularly when combined with cytotoxic chemotherapy. The antiangiogenic effect can be achieved with monoclonal antibodies, such as bevacizumab, directed against circulating vascular endothelial growth factor (VEGF), or small molecule tyrosine kinase inhibitors, such as AZD2171, directed against VEGF receptors. Vredenburgh and colleagues demonstrated encouraging results in a phase 2 study using bevacizumab and irinotecan. They noted a 61% response rate and a 30% 6-month PFS. Batchelor and colleagues used AZD2171 in patients with recurrent GBM and noted improvement in vascular permeability and edema on MRI in some. Both studies suggest that anti-angiogenic treatment may normalize tumor vasculature and allow improved delivery of cytotoxic chemotherapy to GBM. The adverse effects of anti-VEGF treatment include hypertension, thrombosis, and rare reversible posterior leukoencephalopathy syndrome.

**ANTI-INVASION THERAPY**

Unfortunately, past trials using targeted anti-invasion treatments for GBM have been disappointing. For example, marimastat and prinomastat in combination with temozolomide did not improve patient survival, and the effect of major toxicity was joint pain. This is an area that needs much further research and major improvements in clinical approaches.

**Acknowledgment**
We thank Deborha Cooper for her help with the graphics and other technical issues.

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