



## **Emerging Prognostic Markers in Gliomas**

Aaron S. Wagner, MD

CAP Neuropathology Committee

High-grade glial tumors remain among the most aggressive and refractory malignancies, traditionally having a poor prognosis, few treatment options, and few ways to predict which ones might respond to treatment. However, different molecular, genetic, and immunohistochemical markers are playing an emerging role in guiding treatment and prognosis in these neoplasms. As a result, you may begin to notice several prognostic and therapeutic markers tested in your patients diagnosed with high-grade glial tumors. Three of the more promising markers include specific derangements of the epidermal growth factor receptor (EGFR) pathway, methylation of O6-methylguanine-DNA methyltransferase (MGMT), and 1p19q chromosomal deletions.

The most complex of the three above markers is the EGFR gene and its related downstream markers. Specifically EGFR-vIII mutant receptor is found in many gliomas as well as some lung cancers and breast cancers<sup>1</sup>. Key markers in the cascade of its actions include the phosphoinositide 3-kinase (PI3K) pathway, AKT (serine/threonine protein kinase B), and phosphatase and tensin homolog (PTEN). Some initial studies suggest that patients treated with erlotinib and gefitinib show increased response when tumor cells co-express EGFRvIII and PTEN, or when diffuse EGFR immunopositivity is coupled with absence of phosphorylated AKT. Further studies attempting to confirm these results have been mixed and these assays, while still showing promising potential, remain immature<sup>1,2</sup>.

Many chemotherapeutic agents act by alkylating (the addition of methyl groups) specific areas of guanine in DNA, which causes the appearance of an irreparable C-G mismatch to the cell's DNA mismatch repair machinery and triggers apoptosis. Another DNA repair enzyme, methylguanine methyltransferase (MGMT or AGT), works by repairing alkylated guanine nucleotides and preventing cell death and imparting drug resistance<sup>1</sup>. A new drug, O6-benzylguanine, works by depleting the cell's reserves of MGMT and is used as a chemosensitizer in glial tumor patients. Several studies have also indicated that some tumors naturally express only low levels of MGMT corresponding to

increased sensitivity to the alkylating agent, temozolomide. At this time the ideal methods and levels of MGMT expression to best predict outcome are still being elucidated<sup>1,2</sup>. As progress in these areas is made, more and more labs may join some larger centers that routinely report MGMT activity today.

Finally, the most widely used marker in glial tumors is the combined loss of chromosomal arms 1p and 19q in patients with anaplastic oligodendrogliomas. This genotype imparts a clear therapeutic and survival benefit to patients treated with radiation therapy and alkylating regimens including temozolomide and procarbazine-lomustine-vincristine (PCV) therapy. Additionally, recent work has suggested that 1p/19q loss in lower grade oligodendrogliomas and mixed gliomas predicts better response and/or survival. Interestingly, the mechanism for this response is unknown, despite intensive ongoing work<sup>1</sup>. Today clinicians should expect to see 1p19q testing in all tumors that have histologic evidence of oligodendroglial differentiation to help clinicians and patients fine tune prognosis and predictive estimates.

These markers and others may someday lead to new therapeutic agents and strategies similar to those employed in the management of other neoplastic lesions such as gastrointestinal stromal tumors (GISTs), chronic lymphocytic leukemia, and breast and prostate carcinomas.

#### References:

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