Pathology: Commonly Monitored Glioblastoma Markers: EFGR, EGFRvIII, PTEN, and MGMT

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KEYWORDS

• EGFR • EGFRvIII • PTEN • MGMT • Glioblastoma

In 1926, Bailey and Cushing established the first widely accepted classification scheme of astrocytic neoplasms.[1] Since then, neuropathologists have worked to improve this classification system to guide clinicians with diagnostic and prognostic information. Recent advances and discoveries in immunocytochemistry markers, radiographic imaging modalities, and genetic/molecular markers have helped further characterize these tumors. Many of these advances have not yet changed the management of astrocytic neoplasms. Nevertheless, they have provided a wealth of information and continue to challenge current understanding of tumor biology and patient management while providing insight into possible novel therapeutic strategies.

The most common astrocytoma, glioblastoma (GB), is also the most malignant primary brain tumor in adults.[2] There are 2 types of GBs distinguished by their origin and molecular phenotype: primary (de novo) and secondary tumors. De novo cases represent the majority (>90%) of GB patients and develop rapidly over the course of weeks, presenting as a grade IV tumor. Secondary GBs present as lower-grade gliomas (grade II or III) and eventually progress to grade IV. Regardless of its classification, once a diagnosis of GB has been made, the overall median survival time for patients treated with surgery and concomitant radiation plus temozolomide, followed by adjuvant temozolomide, is approximately 15 months.[3]

It is still unclear which molecular and cellular alterations transform a normal cell into tumorigenic GB cells. Previous research has begun to identify and elucidate the molecular pathways that are often perturbed in GBs. These signaling pathways can be therapeutically beneficial because they not only help identify and classify glioma tumors but also may provide novel targets for therapy. This article highlights and reviews 4 important GB molecular markers: epidermal growth factor receptor (EGFR), EGFR variant III (EGFRvIII), phosphatase and tensin homolog deleted on chromosome 10 (PTEN), and O^6-methylguanine-DNA methyltransferase (MGMT).

EGFR

Background on EGFR

EGFR is a cell surface transmembrane tyrosine kinase (TK) receptor that belongs to a family of 4 related receptors: ErbB1/EGFR, ErbB2/Neu/Her2, ErbB3/Her3, and ErbB4/Her4.[4] All members of this family contain 3 basic components: an extracellular ligand-binding domain, a transmembrane portion, and an intracellular TK domain.[5] Upon the binding of a ligand, the receptor transforms from an inactive monomer into a catalytically active homodimer that autophosphorylates its own C-terminal tyrosines.[6] This dimerization stabilizes the active receptor confirmation and generates a docking site for proteins to be phosphorylated

Disclosures: No conflicts of interest.
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Neurosurg Clin N Am 23 (2012) 237–246
doi:10.1016/j.nec.2012.01.011
1042-3680/12/$ – see front matter

by the now-active TK domain. Activation of EGFR leads to phosphorylation of downstream proteins, including phosphatidylinositol 3-kinase (PI3K), AKT, RAS, RAF, and mitogen-activated protein kinases. These downstream proteins have been associated with cell division, migration, adhesion, differentiation, and apoptosis, making EGFR an important player in tumorigenicity.[7]

EGFR signaling has been implicated in the pathogenesis of many human cancers, including head and neck, ovarian, cervical, bladder, esophageal, gastric, breast, endometrial, colorectal, and GB.[8,9] Often, EGFR expression or activity is enhanced in tumors through gene amplification, aberrant activity through autocrine overproduction of the receptor ligands, or mutations to the *EGFR* gene. In GBs, EGFR is overexpressed in approximately 40% to 50% of cases, and clinical and research studies show that tumors with overexpressed or amplified *EGFR* exhibit worse prognosis, increased tumor aggressiveness, and resistance to therapeutic treatments.[4] Furthermore, in vitro studies have shown increased resistance to radiation therapy in immortalized GB cell lines stably transduced with EGFR.[10,11] *EGFR* gene amplification is 5-fold higher in primary GBs compared with secondary tumors, and EGFR overexpression occurs in approximately 60% of primary cases, although this is found only in 10% of secondary GBs.[12]

Because aberrant EGFR activity plays an important role in malignant transformation, new therapeutic strategies have been developed targeting this gene. For instance, small-molecule TK inhibitors and monoclonal antibodies (mAbs) have been studied in clinical trials. Recently, newer treatments, including RNA-based therapies, ligand-toxin conjugates, and radioimmunoconjugates, have had promising preclinical results.[13–19]

EGFR Inhibitors Targeting the ATP-Binding Pocket

One of the earliest and most common methods of inhibiting EGFR is the use of small molecules that bind to the ATP-binding pocket of the TK domain, thereby preventing autophosphorylation and subsequent activation of the signal mechanism. Imatinib and lapatinib are two examples of molecular inhibitors of tyrosine kinases (others include erlotinib and gefitinib) that were originally designed to target similar TKs (ABL and HER2, respectively) but were found to also inhibit EGFR. Phase I and II trials investigating these inhibitors in GBs have demonstrated only modest clinical effects.[20,21] Even with small molecules that specifically inhibit EGFR, such as erlotinib and gefitinib, the clinical results are modest. In a phase II trial, 38 recurrent GB patients were treated with erlotinib monotherapy after radiotherapy. Patients were found to have a median progression-free survival (PFS) of 8 weeks, with only 3% of patients meeting a target goal of PFS at 6 months.[22] A separate, randomized phase II trial of 110 patients with progressive GB after prior radiotherapy showed that only 11.4% of erlotinib-treated patients with recurrent GB had PFS after 6 months compared with 24% of patients in the control arm treated with temozolomide or carmustine (BCNU).[23] No significant difference in overall survival was observed between the 2 treatment arms. When gefinitib was used as the main treatment in a phase II trial, 6-month PFS occurred in 13% of the GB patients with no significant increase in median overall survival compared with historical controls.[24,25] In another phase II trial involving 98 newly diagnosed GB patients treated with adjuvant gefitinib postradiation, the overall survival at 1 year was 54.2% and PFS at 1 year was 16.7%, results that are not significantly different compared with historical controls.[26] In order to enhance the efficacy of gefitinib, a combinational study with an inhibitor to a mammalian target of rapamycin (mTOR) was also conducted. mTOR is located downstream of 2 well-known EGFR substrates, AKT and PI3K, and by combining the 2 inhibitors the goal was to inhibit the PI3K/AKT signaling pathway in concert with EGFR antagonism. In a phase I trial, patients with recurrent, high-grade gliomas treated with gefitinib and sirolimus (an mTOR inhibitor) showed that 44% of the patients achieved either partial response or stable disease, with PFS similar to that in a separate phase II study involving gefitinib treatment alone.[25,27] More recently, the phase II trial of erlotinib plus sirolimus in adults with recurrent GB showed negligible activity.[28] Another study using gefitinib and everolimus treatment in 22 patients with recurrent GB showed 36% of patients with stable disease and 14% with a partial response but only one patient with PFS at 6 months.[29]

Monoclonal Antibodies Blocking EGFR Ligand Binding

Another method of inhibiting EGFR activity is by blocking the ligands that bind to the EGFR (epidermal growth factor, transforming growth factor, heparin-binding epidermal growth factor–like growth factor, amphiregulin, betacellulin, epiregulin, and epigen). mAbs, such as cetuximab and nimotuzumab, were devised to compete with EGF binding and were shown in vitro to decrease the downstream signaling cascade of EGFR.