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Using molecular information to guide brain tumor therapy

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A deeper understanding of the role of specific genes, proteins, pathways and networks in health and disease, coupled with the development of technologies to assay these molecules and pathways in patients, promises to revolutionize the practice of clinical medicine. We are moving from relatively broad pathologic diagnoses, population-based risk assessments and relatively nonspecific therapies into an era of predictive individualized care based on molecular classification and targeted therapy. Patients with the most intractable diseases seen by neuro-oncologists, such as primary brain tumors, are set to benefit from these developments.

Brain tumors are the leading cause of cancer death in children and the second most common cause of cancer death in young adults, and they account for a high proportion of cancer deaths in older adults.[1] Patients with glioblastoma—the most common form of malignant primary brain tumor in adults—have a median survival of around 15 months from the time of diagnosis, even with aggressive surgical excision, radiation and chemotherapy.[2] New drugs that block specific molecular targets are being developed, and molecular information on clinical samples is becoming a reality. Incorporating these complex molecular data into clinical treatment decisions, however, remains a considerable challenge.

Part of this challenge lies in redefining the nature of the diagnosis, which currently relies on the classification and grading of tumors according to their microscopic resemblance to a presumed CNS cell of origin or its developmental precursor. This system has proved to be quite useful for predicting the overall survival for groups of patients with specific types of brain tumor, but provides limited insight into the underlying molecular lesions. Clinically relevant subsets that are microscopically identical, but might nevertheless differ significantly in their clinical course and response to therapy, cannot be identified by this system.

Because patient inclusion in clinical trials currently relies on histological classification, potentially effective treatments that might be of benefit to specific patient subsets will not be recognized.[3] Considerable progress towards identifying relevant subsets has been made, however. Glioblastoma is a molecularly diverse disease with distinctive patterns of chromosomal gain or loss, and oncogene or tumor suppressor gene alteration, which confer significant differences in patient survival and potentially necessitate different treatments. Extensive molecular data about gene mutations, POLYMORPHISMS, chromosomal alterations, global patterns of methylation, acetylation, splicing and protein networks will become available. How will this information be used in the clinic?

Several notable success stories indicate that molecular data can be incorporated into clinical decision making for brain tumor patients. Cairncross, Louis and others demonstrated that anaplastic oligodendroglioma patients who have tumors bearing chromosome 1p loss almost always respond to procarbazine, lomustine and vincristine (PCV) chemotherapy, and those who have tumors with combined 1p and 19q loss in the absence of other detectable molecular lesions have durable clinical responses to chemotherapy.[4] This indicates that incorporation of genetic data might help guide neurologists and neuro-oncologists to decide which of their patients can potentially be spared from radiation therapy.

The recent work of Hegi, Stupp and colleagues showed that glioblastoma patients with tumors showing methylation in the promoter of the O^6-methylguanine-DNA methyltransferase (*MGMT*) gene benefit from temozolomide, whereas patients whose tumors lack this alteration do not experience the same beneficial effects.[5] Using a more global genomic strategy, Pomeroy and colleagues have suggested that combining gene expression profiles with clinical data might help to identify which medulloblastoma patients are most likely to have a favorable response to radiation and chemotherapy.[6,7]

The concept of 'oncogene addiction' is also central to strategies for selecting patients who are most likely to benefit from targeted molecular therapy.[8] Tyrosine kinases and other key

regulators of intracellular signaling are commonly overactive in cancer, resulting in persistent signals that promote tumor growth and invasion. There is evidence that tumor cells become 'addicted' to these persistent signals, making them potentially vulnerable to targeted attack by small molecular inhibitors. In glioblastoma, one such target, the epidermal growth factor receptor (EGFR) tyrosine kinase, is commonly amplified, overexpressed, or both, often in association with expression of a chronically activated mutant receptor (EGFRvIII). EGFR and EGFRvIII promote persistent activation of downstream signaling pathways, including the Ras/ERK and PI3K/Akt pathways, which have a vital role in glioblastoma development and progression. Glioblastomas also frequently lose expression of phosphatase and tensin homolog (PTEN), a tumor suppressor protein and negative regulator of the PI3K/Akt signaling pathway, further potentiating dependence on this pathway.

A recent study investigated which patients with malignant glioma are most likely to benefit from the EGFR kinase inhibitors gefitinib or erlotinib.[9] The clinical response to EGFR kinase inhibitors was strongly associated with coexpression of EGFRvIII and PTEN by the tumor. These findings were validated in a dataset of 33 patients treated at a different institution. Furthermore, in a series of isogenic model systems, EGFRvIII sensitized glioblastoma cells to EGFR kinase inhibitors, and loss of PTEN conferred resistance to drug-induced cell death.

This study demonstrates that malignant glioma patients can benefit from targeted kinase inhibitor therapy, and that molecular stratification might be used to identify patients who are most likely to respond to this approach. It highlights some important challenges, however. Patients with chronic myeloid leukemia who respond to the Abl kinase inhibitor imatinib, and lung cancer patients who respond to the EGFR kinase inhibitor erlotinib, might develop resistance to therapy through selection for cells with mutations that render their tumors insensitive to the kinase inhibitor.[10–12] It is not yet clear whether this will occur in malignant glioma patients treated with molecularly targeted therapies. Glioblastomas display striking intratumor molecular heterogeneity, raising the question of whether treatment with tyrosine kinase inhibitors will select for tumor cells lacking the relevant molecular targets or 'oncogene addiction' states. Understanding the molecular mechanisms underlying these phenomena could enable the development of more effective combination therapies to induce long-term disease suppression or even cure.

We can begin to envisage a roadmap for using molecular information to guide brain tumor therapy. First, we need to identify promising new molecularly targeted therapies that demonstrate a clinical benefit, even if it is only in a small subset of patients. Next, we need to refine molecularly based hypotheses regarding the mechanisms of sensitivity and resistance by incorporating evolving understanding of the relevant pathways. These hypotheses need to be tested in well-designed clinical trials, and tissue needs to be collected and analyzed to determine the molecular correlates of tumor progression and treatment response. In parallel, we must examine and define the mechanisms of sensitivity and resistance using well-designed experimental model systems. Combination therapies can then be designed on the basis of these mechanisms and the molecular correlates. These steps are likely to have a crucial role in making long-term disease suppression or cure a realistic prospect for patients with brain tumors.

GLOSSARY

POLYMORPHISMS
Different genetic variants at the same locus in the same population, with a relatively infrequent variant occurring more frequently than can be explained by recurrent mutations

Competing interests
The authors declared they have no competing interests.

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