Biology and Treatment of Malignant Glioma

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A large number of oncogenes have been identified as aberrant in gliomas, but only the erbB oncogene (gene encoding the epidermal growth factor receptor [EGFR]) is amplified in an appreciable number. The loss or

Gliomas are rare compared to cancers of the breast, lung, or colon, but few malignancies are more devastating. While no therapeutic breakthroughs have occurred, the treatment of glioma is improving. Surgical care is improving. Magnetic resonance imaging and intraoperative mapping studies are leading to safer, more complete resections. With scan-guided stereotactic biopsy, unresectable tumors can be sampled safely and precise diagnoses established in most instances. Improvements in radiotherapy, such as three-dimensional (3D) conformal treatment, that reduces the volume of normal tissue irradiated, promise to lessen the risk of delayed neurotoxicity without sacrificing the tumor-controlling benefits of higher doses of radiation.

Chemosensitive subsets of high-grade glioma (eg, oligodendroglioma) are being identified, and medical management is improving in other respects, as well. A growing network of oncologists and neurologists cognizant of the special needs of patients with brain tumors, together with the emergence of multidisciplinary brain tumor treatment centers, are enhancing patient care.

Radiotherapy and Radiosurgery for Malignant Gliomas
As highlighted by Drs. Shapiro and Rankin Shapiro, the treatment of malignant glioma begins with surgery.[1] Where feasible neurologically, every effort should be made to achieve a complete resection[2]few would argue that a biopsy procedure, intentionally foregoing tumor removal, is appropriate for patients with readily resectable high-grade lesions. Surgery is then followed by involved-field radiotherapy. Doses in the range of 60 Gy are probably superior to lower ones,[2] although a randomized controlled trial specifically designed to compare the efficacy of various doses of radiation for malignant glioma has yet to be conducted. Because radiotherapy is effective, brachytherapy and stereotactic radiosurgery were promoted to increase tumor dose, while promising to spare normal tissue. Brachytherapy may modestly improve local tumor control, but severe toxic reactions in some patients and the need for reoperation in 50% have undermined a technique that appeared promising (and was used widely) less than a decade ago. Stereotactic radiosurgery, being both noninvasive and completed in a single treatment, has replaced brachytherapy, even though higher doses of irradiation can be delivered with implants. Tumor size and location restrict the effectiveness of radiosurgery, and as tumor size increases, the dose of radiation administered by stereotactic radiosurgery decreases. Any conclusion about the role of stereotactic radiosurgery in the initial treatment of malignant glioma must await completion of a randomized controlled trial by the Radiation Therapy Oncology Group. However, the issues that undermined brachytherapy, namely, selection bias and radionecrosis, may limit the utility of this new technique as well.[3] In our view, measures that enhance the therapeutic ratio of radiotherapy for glioma by reducing its neurotoxicity (eg, 3D conformal treatment) may be substantially more rewarding than measures that attempt to enhance its efficacy by increasing dose.

Treatment With Chemotherapy
Many consider adjuvant chemotherapy with a nitrosourea to be standard treatment for patients with malignant glioma. Two Brain Tumor Study Group trials in the 1970s demonstrated that adjuvant carmustine (BCNU [BiCNU]) prolonged survival in a subset of patients (approximately 15%). Although the addition of chemotherapy did not prolong median survival in a meaningful way in either study, a combined analysis of the data published by Green and colleagues in 1980[4] disclosed an unequivocal survival benefit with the addition of BCNU. Unfortunately, no prognostic factor or clinical feature reliably predicts which patients will benefit from adjuvant chemotherapy. This, combined with the fact that treatment is usually well tolerated, has led to the recommendation by some that chemotherapy be administered to all patients. The alternative viewpoint of withholding adjuvant chemotherapy because its benefit is small has been advocated by others. Most agree that elderly patients (≥ 65 years old) or those with poor function
(Karnofsky performance score < 50) rarely benefit clinically from adjuvant BCNU. The observation that oligodendrogial tumors often respond to chemotherapy is one of the more intriguing developments in neuro-oncology in recent years.[5] First recognized in high-grade anaplastic tumors, it has since become apparent that symptomatic low-grade oligodendrogliomas respond to chemotherapy as well. The combination of procarbazine, CCNU, and vincristine (PCV) has become standard therapy for these tumors, although the list of DNA-damaging agents to which oligodendrogliomas respond now includes BCNU, melphalan (Alkeran), diaziquone (AZQ), thiotepa, dacarbazine (DTIC), dibromodulcitol (Mitolactol), temazolomide (Temodar), and regimens containing cisplatin (Platinol). Perhaps as a consequence of their cell of origin, unique alterations of chromosomes 1p and 19q,[6] intact p53 genes, or other factors, gliomas with oligodendrogial differentiation are sensitive to drugs that alkylate DNA.

The drug-sensitive nature of oligodendrogial tumors has led our group to explore the use of aggressive chemotherapeutic strategies at diagnosis in an effort to postpone cranial irradiation. Although radiotherapy is effective, unavoidable long-term cognitive toxicities do result when large treatment fields are required to encompass the tumor. Oncologists will gradually fine-tune chemotherapies for oligodendroglioma but have yet to crack the astrocytoma/glioblastoma barrier. Effective systemic therapies for the latter may not evolve until these cancers are understood at a basic level.

**Genetic Abnormalities**

Drs. Shapiro and Rankin Shapiro summarize the multiplicity of cytogenetic abnormalities that have been observed in high-grade astrocytomas and glioblastomas and allude to the distinct molecular pathways of high-grade glioma now emerging. It has become apparent that oligodendrogliomas not only are chemosensitive but also have unique genetic derangements that distinguish them from astrocytic neoplasms. At least two molecular pathways to the formation of glioblastoma exist.[7] Inactivation of p53 and amplification of epidermal growth factor receptor (EGFR) are mutually exclusive genetic alterations: approximately one-third of glioblastomas harbor p53 mutations and another third have EGFR amplification.

In general, glioblastomas with p53 mutations occur in younger patients and evolve from low-grade astrocytomas, while those with EGFR amplification occur in older patients and typically arise de novo. Perhaps these molecular differences will have therapeutic implications. Indeed, the oligodendroglioma story suggests that the response of gliomas to treatment is not a chance event, but rather, a predictable phenomenon governed by histogenesis, molecular pathways, or both. We envision an exciting future for oncologists treating glioma. Existing therapies will be used more rationally and with greater effectiveness, while new drugs that block signal transduction, inhibit angiogenesis, or impede glioma cell invasion will compensate for the molecular abnormalities that give rise to uncontrolled glial cell growth.

**References:**


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