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Central Nervous System Tumors: What Have We Learned and Where Are We Heading?

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After many years of diligent research, great scientific progress, and numerous clinical trials, the problem of brain tumors remains one of the most challenging issues in neurobiology. As time progresses, the scope of the brain tumor problem seems to be widening. Hardly anyone has escaped being touched by a brain tumor in a friend, loved one, or relative, and considerable evidence exists that would lead one to believe that the actual incidence of brain tumors may be increasing.[1]

For many years central nervous system tumors have been the second most common type of tumor in children, and they continue to play an important role in adults of all ages. It is especially sobering to note epidemiologic studies that show that the age-specific incidence of malignant primary tumors of the brain (glioblastomas) increases with increasing age.

Pathogenesis, Molecular Biology, Laboratory Studies, Human Studies, and Clinical Trials: What Have We Learned?

The existence in the normal adult human brain of stem cells that can proliferate into any kind of glial cell, and even into neurons, has shed new light on the possible pathogenesis of primary brain tumors. These discoveries highlight the importance of developmental neurobiology in our understanding of the factors that produce primary parenchymal tumors of the brain and spinal cord. Molecular biology has shown us that both tumor oncogenes and tumor suppressor genes play a role in the development of brain tumors, as Michael D. Prados, MD, and colleagues discuss in their article in this issue.[2] The current hypothesis is that most such tumors originate from a stepwise progression of genetic events related to the expression of these genes and their gene products over time.

A number of cell surface receptors and their potential regulation also may play an important role, as can the blocking of other receptors. Both processes are directly involved in signal transduction within the cell that is an essential factor in the neoplastic process. Growth factors, cytokines, phosphorylases, and signaling pathways within the cell, from the surface receptors to the nucleus, all are being studied with regard to their respective contributions to the pathogenesis of common primary brain tumors.

The concept of apoptosis in the central nervous system also has been studied, and the disturbance of normal apoptotic mechanisms in tumor cells and their possible restoration as a means of therapy both are under investigation.

The blood vessels within primary

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brain tumors have been recognized for some time as being different from normal cerebral blood vessels, and the characterization of tumor vessels and the mechanisms by which they develop are a major focus of current attention. This is particularly the case with antiangiogenesis factors, which now may have reached the stage of being potential agents for therapy.

Two basic aspects of brain tumor biology have hampered previous attempts at therapy; one relates to what we have learned about cell cycle kinetics, and the other is what we know about the ability of tumor cells to migrate and invade through normal brain. Kinetic studies have shown that a significant proportion of the population of a brain tumor at any given time is in a resting state, relatively immune to many of our therapeutic modalities. We also know that tumor cells can invade the normal brain substance and that this invasion process involves the elaboration of proteases and the alteration of cellular adhesion molecules.

These processes permit tumor cells to travel far from the epicenter of an obviously diagnosed brain tumor. Unfortunately, these cells appear to be relatively insulated from therapeutic modalities because they are outside the blood–brain barrier and are frequently in a dormant state with regard to proliferation. These features have stimulated some investigators to evaluate methods of altering the blood–brain barrier so that certain chemotherapeutic agents can reach these protected cells.

Carefully performed clinical studies have shown us that radiation therapy significantly benefits patients with malignant primary brain tumors, and conventional fractionated radiation therapy remains the cornerstone of adjunctive therapy.

No single study has adequately addressed in a prospective fashion the question of whether cytoreduction, or the removal of the bulk of a particular brain tumor, can enhance patient survival. However, virtually every study that has looked at this concept in a retrospective fashion has shown that for malignant gliomas, the reduction of the tumor burden is an important part of the overall therapeutic endeavor. This knowledge has spurred the use of sophisticated localization studies to protect normal brain during the performance of as radical a surgical removal of intrinsic tumors as possible. Electrophysiology, functional imaging, and computer-guided stereotactic surgical devices all have helped neurosurgeons achieve these goals.

Where Are We Heading?

We know that many primary brain tumors contain a significant oligodendroglial component. Therefore, the effective therapy for oligodendrogliomas—namely, the combination of procarbazine, cyclophosphamide, and vincristine (PCV)—has been employed with great impact and with clear evidence of benefit, making this form of combination chemotherapy the most effective medical management currently available. Many single agents and some combination therapies have been tested in clinical trials, but none has been as consistently effective as PCV in appropriately selected patients.[3]

In pediatric brain tumors the adjunctive use of chemotherapy has provided good long-term control of some tumors and has allowed the dose of radiation needed to be significantly reduced, thus avoiding the undesirable side effects of radiation therapy on the immature brain.

New delivery systems for chemotherapeutic agents are currently being tested. These include polymers that slowly release locally implanted chemotherapeutic agents and the use of direct injection of both chemotherapeutic agents and viral agents used for gene therapy into a tumor with diffusion/convection delivery.

The advent of gene therapy some years ago sparked several strategies for using this modality for treating brain tu-

mors. Such strategies include the insertion of "suicide" genes, the delivery of genes that cause differentiation, the insertion of tumor suppressor genes, and other approaches that are ingenious but unfortunately have not yet been fully effective.

Immunotherapy continues to be applied in the treatment of brain tumors with the use of interferon, interleukin-2 (IL-2), and other interleukins and the development of a variety of antibody techniques for targeting malignant tumor cells.

The development of practical methods for providing focused radiation therapy has added another adjunctive modality for the treatment of brain tumors. These methods include stereotactic radiotherapy and "radiosurgery" using either the gamma knife or a suitably altered linear accelerator. In addition, interest continues in the use of boron neutron capture therapy for malignant brain tumors, and efforts in photodynamic therapy are ongoing. Both techniques are currently undergoing limited therapeutic trials with modifications aimed at overcoming some of the problems that occurred in previous attempts to take advantage of these methods.[4]

With the clear demonstration of biologic features such as tumor cell invasion in normal brain and polyclonal resistance developing within treated malignant brain tumors, it is evident that only multimodality therapy will succeed in the future. The prospect for the future is that we will continue to capitalize on the technical advances made and the scientific knowledge obtained so that we finally achieve a satisfactory measure of control over these challenging lesions.

References

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