Chemotherapy for Brain Tumors

By S. Clifford Schold, Jr, MD [2]

Traditionally, cytotoxic drugs have played a limited role in the treatment of brain tumors, but important advances in chemotherapy have occurred during the past decade. Certain central nervous system (CNS) malignancies are

I can only supplement the thorough and accurate review by Drs. Pech, Peterson, and Cairncross. They give relatively little space to the most common primary central nervous system (CNS) neoplasms, anaplastic astrocytomas and the glioblastomas, because chemotherapy for these tumors has had limited success. However, it is important to recognize that occasionally these notoriously chemoresistant tumors have a dramatic response to currently available agents. Although it is unclear why only a minority of these tumors are sensitive, there may as yet be undiscovered phenotypic traits of an individual neoplasm that predict sensitivity.

One trait that has been identified is the expression of O⁶-alkylguanine-DNA alkyltransferase (AGT) in tumor tissue. High activity of this DNA repair protein appears to predict resistance to the nitrosoureas and related drugs that alkylate at the O⁶-position of guanine. Low AGT expression correlates with sensitivity.[1] The full story will undoubtedly be more complex, but it is an important observation because an AGT inhibitor, O⁶-benzylguanine, has entered clinical trials. This compound has the potential to render previously resistant tumors sensitive to alkylating drugs.[2] Identification of other proteins that produce drug resistance may allow us to tailor treatments to measurable characteristics of individual tumors.

CNS Lymphomas

The only minor point on CNS lymphomas that I would quibble with is the authors’ suggestion that perhaps 40% are exquisitely sensitive to corticosteroids. In my experience, virtually all CNS lymphomas are sensitive to steroids, but the degree of sensitivity varies widely. It is true that a very small percentage are so sensitive that the tumors disappear for prolonged periods, and other patients show only modest clinical improvement and less obvious lesions on imaging studies. It is also true that administering steroids can mask the target for a biopsy, but of course there are patients who are so neurologically symptomatic that steroids cannot be withheld.

Medulloblastomas

Medulloblastoma has been a frustrating tumor for neuro-oncologists who have investigated the use of chemotherapy. On the one hand, responses to chemotherapy are common in the setting of recurrent disease. On the other hand, adjuvant trials of combined radiation and chemotherapy have produced disappointing results. Most likely, the wrong drugs were used in the adjuvant studies since medulloblastomas are generally not very sensitive to nitrosoureas. Platinum-based regimens appear to be far superior. In addition, the results of preradiation chemotherapy in very young children have been disappointing.[3] It is likely that medulloblastoma in a child under age 3 years is a much more malignant tumor than the same tumor in an older child. The results of chemotherapy in this select population, then, may not be reflective of the overall drug sensitivity of this family of tumors.

Oligodendrogliomas

The oligodendroglioma story is a fascinating one. It is clearly a chemosensitive tumor, and, in retrospect, many of the responses seen in malignant brain tumors when chemotherapy was first tested were probably in tumors of oligodendrogial lineage. The biggest problem now is determining whether or not a tumor is oligodendrogial. There is no histologic gold standard or diagnostic immunostain to tell the pathologist that an anaplastic primary brain tumor is oligodendrogial. This remains a judgment call.

In recent years, because of growing awareness of the chemosensitivity of these tumors, neuropathologists have become more attuned to their diagnosis and consequently are more likely to describe oligodendrogial features. It is unclear how much of an oligodendrogial component in a tumor is needed to predict drug sensitivity. These issues will be sorted out over the next few years, particularly as new lineage markers are developed.
Chemotherapeutic Strategies
The authors have also accurately summarized new strategies for improving the efficacy of chemotherapy. High-dose chemotherapy may improve outcome in selected chemosensitive tumors. Improved delivery techniques, either by pharmacologic manipulation of the blood-brain barrier or by local application of cytotoxic agents, should be thoroughly investigated. As mentioned earlier, biochemical mechanisms of drug resistance should be explored and, if possible, modulated to enhance sensitivity. Finally, new drugs, particularly those that are targeted to the unique molecular characteristics of a tumor, should be developed and thoroughly explored.

Much progress has been made in the last decade in treating selected forms of brain tumor. I expect even more rapid and dramatic advances in the years ahead.

References:


Source URL: http://www.physicianspractice.com/review-article/chemotherapy-brain-tumors-0

Links: