Current Trends in the Chemotherapy of Brain Tumors with Special Reference to Glioblastomas*

CHARLES B. WILSON, M.D., AND TAKAO HOSHINO, M.D.
Division of Neurological Surgery, University of California School of Medicine, San Francisco, California

Glioblastomas account for one out of every four brain tumors, yet despite efforts to treat them by total operative removal, radiation therapy, and administration of a variety of chemotherapeutic agents, we know of no instance in which such treatment has resulted in cure. However, surgical experience does indicate that the most radical operative procedure that is consistent with maintenance of neurological function accomplishes more for patients, in terms of survival, and achieves a lower operative mortality and better postoperative condition than does a less extensive operation.25,38 In most large series, patients harboring glioblastomas have a median postoperative survival of 6 months, and few survive beyond 18 months.25,38,53 Postoperative radiation therapy usually lengthens survival by several months, and is believed by some authors to allow long-term survival. However, others maintain that radiation improves neither the quality nor the duration of survival in patients with glioblastomas.90 Because occasional longer-term survival follows treatment by operation alone, long-term survival of isolated cases treated by any adjuvant therapeutic modality lacks significance.21

In 1964, one of us (CBW) reviewed reports of brain tumor chemotherapy appearing during the preceding 12 years.107 As judged by clinical improvement during the course of therapy, several antitumor agents were beneficial in approximately one-half of the treated patients. In a more recent review, Batzdorf3 found no significant difference in the survival of 145 operative patients treated with chemotherapeutic agents and 43 patients undergoing operation alone with or without postoperative radiation. While chemotherapy may improve the quality of survival, apparently to date it has failed to lengthen the lives of patients with glioblastomas to any statistically significant degree.

The neurosurgeon's recently acquired interest in the chemotherapy of brain tumors stems from a recognition of two facts. First, with the exception of a few low-grade and favorably situated gliomas, tumors arising within the brain have defied surgical cure. Second, for the first time cancer chemotherapists can speak in realistic terms about the cure of solid tumors outside the brain.

In the following review we will discuss certain factors unique to brain tumor chemotherapy and principles of chemotherapy applicable to the central nervous system. A historical review of specific agents and routes of their administration will serve as a background for a discussion of brain tumor chemotherapy in the light of presently available agents and past experience with them.

Anatomical Characteristics of Glioblastomas

Glioblastomas infiltrate the surrounding brain84 and almost invariably are larger and more extensive than suspected by clinical and radiological findings.12 At autopsy, at least one-half of the glioblastomas are found to involve both cerebral hemispheres by extension across cerebral commissures, primarily the corpus callosum.60,61 The high frequency of bilateral involvement has important implications for surgical removal as well as regional and local chemotherapy.

Cerebral edema of some degree invariably surrounds the periphery of glioblastomas. Ultrastructural characteristics of this edema indicate its localization predominantly in the extracellular space and white matter.2 Such studies further indicate that at least some of the extracellular fluid originates from within astrocytes, a rupture of cell membranes releasing the fluid into the extracellular compartment. Edema not only contributes to the

Received for publication December 23, 1968.

* Supported in part by NIH research grant CA-07859-04 and the Naffziger-Guggenhims Fund, University of California Medical Center, San Francisco, California. Presented at the Fourth Annual Clinical Cancer Conference, San Francisco, November 9-10, 1968.
space-occupying effects of the tumor, but represents disruption of the normal barrier mechanisms imposed between the vascular compartment and extracellular space within the brain. Present diagnostic methods do not permit clear distinction between edema and neoplastic tissue, and reduction in the volume of either element reduces the total mass effect of the tumor-edema complex. Any therapeutic maneuver resulting in temporary clinical improvement, particularly when survival is not lengthened also, must be suspected of favorably influencing edema rather than the neoplasm. Disruption of barrier mechanisms in the vicinity of the tumor has further implications regarding the delivery of a chemotherapeutic agent to the tumor cells and exposure of the edematous brain to agents excluded from undamaged brain by intact barriers.

Glioblastomas possess a complex vascular supply. Hardman studied the angio-architecture of gliomas in a classic paper29 and his observations have been supplemented by subsequent postmortem studies.69,92 Conventional arteriography fails to give an entirely accurate picture of tumor blood supply because injection alters normal flow and contrast media are viscous and heavy.65 Blood vessels within a glioblastoma are characterized by tortuosity, aneurysmal dilatation, glomeruloid sprouts, endothelial proliferation, and medial hypertrophy. Although Hardman found no true arteriogenous anastomoses, capillary dilatation and sinusoidal enlargement produced a similar effect. Characteristics of blood vessels within a tumor become significant whenever chemotherapy by intravascular administration is considered. Arteriography clearly indicates an abundance of blood vessels within many glioblastomas, and rapid transit of blood through such tumors is a second common characteristic. However, by analogy with cerebroarteriovenous malformations, the presence of large blood vessels and a rapid rate of blood flow offer no assurance of adequate perfusion through surrounding tissues, whether normal or neoplastic.

**Exploitation of Differences Between Brain and Brain Tumors**

In treating tumors within the brain, as elsewhere, the narrow margin of safety between the minimal effective therapeutic dose and the maximal tolerated tissue dose limits the effectiveness of both radiation and chemotherapy. Even when cytotoxic action can be intensified by various potentiating factors, this small therapeutic index usually persists due to a relative lack of specificity of these agents for the tumor cell.70 The rationale of combining different therapeutic modalities is based on the assumption that simultaneous administration of two or more agents acting at different sites and stages of cellular activity should result in inhibition of a greater total number of tumor cells than would result from administration of a single agent.

With the exception that some tumor cells depend upon an exogenous source of asparagine,70 the nutritional requirements of tumor cells differ in no significant way from those of normal cells, and apparently both types of cells handle these nutrients similarly along the same biosynthetic pathways. Surprisingly, in vitro studies suggest that the respiratory rates of benign brain tumors are high whereas those of glioblastomas are significantly lower. With no apparent distinction, anticancer drugs inhibit the respiration of normal brain and brain tumor cells, and this lack of specificity in vitro corresponds to clinical and pathological evidence of the toxicity of many anticancer drugs on normal nervous tissue.57

Hexose provides the endogenous energy reserve in normal white matter, whereas in vitro studies show that glioblastomas continue to produce lactate at a steady rate after prolonged anaerobiosis. This lactate production far exceeds that expected from hexose breakdown by way of the Embden-Meyerhof pathway.43 Preliminary studies in our laboratory suggest that glial cells may be asparagine-dependent, but with this possible exception, metabolic differences between normal brain and brain tumors cannot be exploited in our present stage of knowledge. Even the finding of an exploitable metabolic difference might be disappointing, since cytologic and cytochemical evidence indicates that within the heterogenous group of tumors classified as glioblastomas marked differences exist not only between tumors but also within an individual tumor.48

Intracerebral synthesis of deoxyribonu-