

# Advances in the Management of Patients with Malignant Brain Tumors\*

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In describing what is new in the management of malignant brain tumors, I shall confine myself largely to chemotherapy and shall outline what we think is important based on our own experience, what we have achieved with single and multiple agents, and where we are going. We have just reviewed our five-year experience and find that chemotherapy, perhaps, is the only thing that is new.

The development of drugs since 1943 has been escalating at a fantastic rate. Today, we can provide the chemotherapist with a wide array of drugs from which to choose.

Several neoplastic diseases are now recognized as being highly responsive to chemotherapy and the list is growing. The first to be recognized was childhood lymphocytic leukemia, then choriocarcinoma, and now testicular carcinoma and Wilm's tumor.

The first consideration for effective brain tumor chemotherapy, as we see it, is that the agent must have optimum lipid solubility or a special transport system. We are convinced that it must penetrate the normal brain to be truly effective, and I shall indicate our reasoning below.

One must achieve an adequate drug level in brain adjacent to the tumor with minimal or no neural toxicity, and the drug must be given frequently enough to produce maximal DNA damage with insufficient time for repair. At the present time, we are studying the rate of DNA damage and repair in a search for combinations of drugs that will give less

than added toxicity and, at the same time, will produce synergistic antitumor effects.

A water soluble compound is excluded by the intact blood-brain barrier and, administered intravenously, the drug attains a high concentration only in the leaky, central portion of the tumor. As the drug moves toward ventricular and subarachnoid cerebral spinal fluid (CSF), the concentration falls very rapidly, so that the active periphery of the tumor is exposed to low concentrations of its drug and for a brief time only. If one gives a water-soluble drug in the CSF, however, it moves quickly across the ependyma into adjacent brain. It does not exit from the normal brain but diffuses through brain into tumor. This would be a reasonable way, then, to give a water-soluble drug.

On the other hand, if one uses a lipid-soluble agent, for example, the nitrosoureas, it crosses capillaries in the normal brain. Obviously, it crosses the tumor's leaky capillaries, so that one has equal drug concentrations in brain adjacent to tumor and in tumor. If one injects a lipid-soluble drug into the ventricle, it crosses the ependyma, instantly goes out through the capillaries of the normal brain, and none of it ever reaches the tumor, unless it happens to be very close. It would be irrational to use a lipid-soluble drug intrathecally. With lipid-soluble compounds, concentration in the tumor is the same as concentration in the brain. We believe that this is important both from the theoretical standpoint and from our own experience.

Our group is interested in developing effective drugs and drug schedules in the laboratory and in bringing these into clinical trials. We started out with a rat glioma; now we have two rat gliomas and three

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mouse gliomas, which we use for drug screening. In the past, we have used reservoirs in pups for intrathecal administration. We can perform intrathecal injections in the rat, so that it provides a model for therapy, either by continuous intra-arterial infusion or by intrathecal injection. We are not limited by the route of administration. It turns out that the models have been extremely useful, not only for screening promising compounds but also for working out drug schedules and routes for administration.

The kinetics of brain tumors are most important. We have studied animal tumors and have completed studies of human tumors *in vivo*. To summarize what we know about a glioblastoma at the present time, we have shown that in a glioblastoma, approximately 30% of viable cells are actively dividing and the other 70% of the cells are nondividing (nonproliferating). The cell cycle, that is, the length of time it takes a glioblastoma cell to go from one mitosis to two cells at the next mitosis, is somewhere in the range of 2½–3 days. Were it not for a very high rate of cell loss, the volume of a glioblastoma would double in approximately one week. This is unrealistic on the basis of clinical observation. We know that the period of time required for the glioblastoma cell to synthesize its DNA is about 9–10 hours and, interestingly enough, it takes an astrocytoma the same period of time.

In our studies, we have used radioactive thymidine, labelled either with tritium or with <sup>14</sup>C. We have documented the intense proliferation seen in blood vessels within a glioblastoma. In all probability, the limiting factor in the growth rate of a glioblastoma is the rate at which the blood vessels can proliferate, because there is good reason to believe that the capillary endothelium cannot divide as rapidly as tumor cells. In brain adjacent tumor, in the absence of tumor cells, because of tumor angiogenesis factor, blood vessels proliferate in advance of invasive tumor.

The brain presents a particular problem. After treatment with an effective chemotherapeutic agent, a dead cell takes up approximately twice as much room as living cell. The result is an increment of edema or swelling of tumor cells and an increase in volume. This increased volume can be detrimental because of the effects of an increase in intracranial pressure. Dead cells must be removed; although these cells are now nonviable, they are still present and therefore act as a mass. We have just completed studies on dead-cell removal and have shown that when one puts

tagged, lethally irradiated cells in brain, muscle, and subcutaneously, brain has a most inefficient, sluggish means of dead-cell disposal. We are convinced, both from pathological studies as well as our own observations, that the brain is relatively inefficient in removing dead cells as opposed to other solid organs. At this period, we often have to use steroids to combat increased intracranial pressure and the question arises as to what steroids do to tumors?

Methyl prednisolone or any of the glucocorticoids will increase the survival of tumor-bearing animals that receive the steroids. Thus, you can increase the survival of a rat bearing a glioma by giving steroids. If one has a control group and a group treated with methyl prednisolone, and they are killed at the same time (in this instance on the 21st day) one finds that the tumors in the control animals vary pretty widely but have a mean weight of 157 mg, whereas the tumors of the animals receiving steroids are much smaller with a mean weight of 36 mg. One can explain this difference in two ways—steroids kill tumor cells and steroids slow down the rate of cell proliferation. We now have evidence that the latter is true. There is no direct oncolytic effect on glial tumors, but the steroid simply puts certain proliferating cells into a nonproliferating state, and it also increases the period of time necessary for a cell to divide, that is, the cell cycle time. This became very important when we checked our own clinical statistics. Were we confusing ourselves in judging drugs by the concomitant use of steroids? To answer the question, we took consecutive patients. One group of patients never received steroids. With an approximately equal number of patients in both groups, we determined how many were chemotherapy responders, probable responders and nonresponders. The concomitant use of steroids did not change the frequency of response to chemotherapy. We have concluded that steroids have one major effect in the brain tumor patient, that of reducing cerebral edema. To date, we have no clinical evidence that they have any effect on tumor cells.

The material that I intend to present is based on a particular group of patients. These are patients who either have tumors recurrent following surgery and radiation therapy or in whom the diagnosis of a malignant tumor could be made without any reasonable doubt and whom we elect to treat by chemotherapy rather than by radiation therapy. In the latter group, we do not insist upon a tissue diagnosis, feeling that the price of obtaining a tissue

diagnosis is to justify the biopsy of a glioblastoma or a brain stem glioma. For reasons that I shall point out, this is more often the case.

Consequently, patients who are eligible for our Phase II trials are those either with recurrent tumors or with primary tumors who are considered candidates for primary chemotherapy without surgical verification. In addition, we treat a small number of patients with metastatic tumors. A phase II trial asks one question: Is the drug effective, that is, does this drug have some activity against the tumor? It asks neither what the cure rate is nor for how long. A phase II study is designed solely for searching out and identifying effective drugs. For a patient to be eligible for this kind of study, he must first be ineligible for other studies in our program. Second, with a pathological diagnosis or an unequivocal radiographic and clinical picture, the patient is deteriorating neurologically. Third, if radiotherapy has been given, it must have been completed at least three months prior to chemotherapy. Dead cells hang around after the completion of radiotherapy, and late improvement can occur following radiotherapy. As a matter of fact, since we have instituted this rule, we have actually confirmed delayed improvement up to three months after radiotherapy. Finally, the patient is expected to live at least two months, and we are sometimes wrong on that estimate, but the patient, or more often his family, understands the complications of chemotherapy. Parenthetically, I can say that we have lost approximately 1% of our patients as a direct result of complications of chemotherapy; our morbidity has been higher. Mortality has remained low because we have means of rescuing the patient who gets thrombocytopenia or leukopenia.

Thirty-four patients were not treated because: 1) we found no evidence of tumor regrowth, 2) we thought that they would live less than two months, 3) they declined treatment after understanding it, or 4) further surgery was elected. In the latter category, a benign fourth ventricle cyst was referred to us as a recurrent brain stem glioma, and we sent the patient back with diagnostic studies to the referring neurosurgeon who removed the cyst. Recently, I removed a nerve sheath tumor of the tenth nerve which had been misdiagnosed as a brain stem glioma and, after radiation therapy, was sent to us for chemotherapy. We have seen a variety of misdiagnosed lesions, emphasizing the need for careful study. In one patient, we thought radiotherapy was the treatment of choice.

To judge the effect of chemotherapy, we use two criteria. We have a third which will probably be added—the EEG (which came as a complete surprise to me). At first, I would not allow our electroencephalographer to charge our patients, because I was convinced that EEG would be valueless, but it did just about as well as a scan in predicting whether a patient was better or worse. We, like others, will be looking to the EMI scanner for a fourth criterion. The two criteria on which our data are based are the clinical status and the brain scan. A patient classed as a responder is better clinically and his brain scan is better. A patient is designated a probable responder if clinical status is: 1) improved and the brain scan is the same, 2) if the clinical status is the same and the brain scan is better, or 3) if both of them remain the same for at least three months in the case of medulloblastomas and glioblastomas and six months for more benign tumors. A nonresponder deteriorates as judged by clinical status and brain scan.

A certain number of patients in our series were nonevaluable. We determined, in retrospect, that patients surviving for less than two months after beginning treatment were not evaluable—again, because of the slow removal of dead cells. Approximately 15% of all responders were considered failures when they returned for their second course of therapy. If a patient receiving a course of chemotherapy is obviously worse six weeks later, it does not mean that the drug is ineffective, because among those patients who eventually turn out to be unequivocal responders, 15% have had an initial deterioration in brain scan and clinical condition. Several patients were nonevaluable because, in the beginning, we were inexperienced. In some, the neurological condition was not clearly deteriorating immediately prior to treatment; others failed to complete one full course; and on five patients, we were unable to obtain an adequate follow-up.

What can we expect in using single drugs? With BCNU (still the best single drug used to date), 27 of our 57 patients showed a response, a rate of 47% over a mean duration of nine months, and this a population of recurrent tumors. CCNU has a response rate of 44% but for a shorter mean duration. Procarbazine, also a powerful drug with a 52% response rate, has a mean duration of six months. We are unable to give an explanation for the fact that when we combine BCNU and vincristine (which should be a good combination because vincristine is not toxic to the bone marrow), we get a response rate of only 45%

over four months. Although BCNU and CCNU are virtually identical and both are highly lipid soluble, BCNU seems to have a clear advantage. Procarbazine is not lipid soluble, but it does proceed rapidly, in high concentration, into CFX. The three most effective single agents, thus, have in common bone marrow toxicity and very rapid entry into brain and into CSF.

What of the patient who receives a first drug and, whether with or without response, then proceeds with a second drug? A response to a second drug is very small, probably for two reasons—one, a possible cross resistance and two, by the time of proceeding to a second drug, the patient is usually in poor condition.

What can be said of tumor types as related to specific drugs? With malignant gliomas and astrocytomas or glioblastomas, the response is similar with all of the three most effective drugs. For ependymomas, BCNU is extremely good, one of our patients responding to BCNU as the second drug administered. The other tumor-specific chemotherapy, which I shall go into later, is the combination of procarbazine, CCNU, and vincristine that seems to be highly effective for medulloblastomas.

As must be well known, BCNU is given intravenously on various schedules; it is quite likely that we do not use the optimal schedule. One of our early patients, a quadriplegic with an ependymoma, had a fantastic response over several months to BCNU, but ultimately could not receive any more due to the development of cumulative bone marrow toxicity. One patient with a malignant astrocytoma, having been treated with BCNU for two years, shows no evidence of tumor regrowth after two and one-half years off treatment. One young boy, who had a recurrent ependymoma of the fourth ventricle with supratentorial metastases, tumor cells in his CSF, and recurrent tumor in his posterior fossa, was treated with BCNU for two and one-half years; he is attending college now with no evidence of recurrent disease after two years off treatment.

The Brain Tumor Study Group has studied BCNU in a phase III trial, taking patients who had had a major craniotomy and removal of a supratentorial glioblastoma. Postoperatively, these patients were not dependent upon steroids and they randomized within three weeks of operation; thus, this is a select group of patients treated in the early postoperative period. Patients who received no further treatment had a median survival of 15

weeks—a little less than four months, which seems to be a little on the low side. Those patients who received only BCNU postoperatively had a median survival of 21 weeks; those who received irradiation therapy had a median survival of 30 weeks; and those receiving BCNU plus irradiation had a median survival of 40 weeks. How do we interpret this? Irradiation and BCNU combined are better than either alone and better than no further treatment after surgery as well. Of the various forms of adjuvant therapy reported for glioblastomas, the most effective is BCNU and irradiation combined following major tumor removal. At the time of this study, about four years ago, BCNU was used because it had been shown to be an active drug in phase II trials.

One of the people in our laboratory became an expert at removing rat gliomas, and we evaluated adjuvant chemotherapy and surgery, using a rat brain tumor model. We asked: Are we giving BCNU at the right time? Should it be given before operation, with the operation, or afterwards? We tried various combinations of BCNU and surgery and in one group, we even added 5-FU to obtain early proliferating postoperative cells. The study showed that there was no combination of surgery and BCNU that was as beneficial as BCNU alone. I could not believe it and we repeated the experiments four times. The experiments defied my prejudice and the basic laws of cell kinetics, and the results have now been submitted for publication. I do not believe, however, that on this basis, neurosurgeons will stop removing glioblastomas, but we did feel encouraged to treat a few human glioblastomas, diagnosed angiographically without histological verification. Of the patients treated in this way, only two harbored primary reticulum cell sarcomas that we called glioblastomas—not a large error.

Procarbazine is a monoamine oxidase inhibitor and patients under treatment, therefore, cannot eat ripe cheese or take certain drugs. One patient, who showed excellent results by brain scan, became irreversibly psychotic, so it is not a perfect drug, but it does move rapidly into the CSF. In one of our first patients, with a recurrent medulloblastoma and a total spinal block, procarbazine alone melted away the mass. Though active against medulloblastomas, procarbazine alone is not as active as a more recent drug combination to be mentioned below. Its activity against malignant gliomas is similar to BCNU.

Single drug therapy for solid tumors is rarely curative in animal or human systems after the tumor

reaches a clinical size. Those people interested in solid tumors, therefore, are looking to combination chemotherapy, using drugs that have qualitatively different toxicity and complimentary mechanisms of action to prevent the emergence of resistance clones, and are combining agents that act on cycling versus noncycling (nonproliferating) cells.

Our first multiple drug protocol involved three drugs: CCNU, which we knew was active and could be given by mouth; vincristine, which was active and did not add toxicity to the bone marrow; and procarbazine, which we thought was an excellent drug. The course was given on a 28-day cycle: CCNU on day 1, procarbazine for the first 14 days, and vincristine twice (days 1 and 8). We obtained a response rate of 57% (I cannot give the median duration, but it has produced some of the most dramatic responses we have seen with medulloblastomas.). We are now persuaded for the first time, that we have something safe enough and effective enough to justify designing a study of combining chemotherapy with radiotherapy for the immediate treatment of verified medulloblastomas. Our response rate here has been well over 75%, but the patients do develop chronic bone marrow toxicity. For example, a little girl who came in with papilledema and huge subfrontal metastases had a normal brain scan two months ago, after receiving procarbazine, CCNU, and vincristine, but due to chronically depressed bone marrow, we are unable to give her more drug and she is experiencing a recurrence.

We tried the combination of Cytoxan® (cyclophosphamide), CCNU, and vincristine. We saw few responses and concluded that this is not an effective combination.

What are the approaches to more effective chemotherapy? We are convinced that drug combinations are the wave of the future. Simultaneously, we are trying to identify new effective single drugs and effective combinations of single drugs. We are now actually putting into practice schedules based on kinetic information, that is, cell cycle and number or percentage of proliferating cells. It may be possible to convert tumor cells that are nonproliferating into a proliferating state in which they are more susceptible to drugs specifically damaging to proliferating cells. Possibly, we can convert some normal cells, such as gut and bone marrow, from their normal proliferating state to a noncycling compartment, particularly bone marrow, so that it will not be devastated by the drugs we use. We do not have a single drug today that is specific for cancer cells and are always on a tight wire between poisoning the host and poisoning the cancer.

We hear a great deal about enhancing immune mechanisms. In the one reported study, patients who were immunized did no better than those who were not. There are some very promising things on the horizon, but at the moment, I see no immediate role for immunotherapy. The successful acceleration of dead cell disposal, in which we are extremely interested, will have some practical application.

In summary, our studies have identified three agents individually active against a variety of brain tumors. Procarbazine belongs in another pharmacological group, but BCNU and CCNU are similar. Combination chemotherapy holds great promise for brain tumor chemotherapy, and one of the two combinations evaluated by us is highly effective against medulloblastomas.