In the last 30 years, while considerable progress has been made in laboratory research of malignant gliomas, fewer clinical breakthroughs can be highlighted. Laboratory research has improved our understanding of the biology, and especially the molecular genetics of this disease. Unfortunately, these successes highlight the difficulties in translating laboratory results into substantive clinical improvements. In part, these difficulties stem from a schizophrenic view of the development and evolution of brain tumors. We believe either that (1) brain tumors are local and therefore the most important research should have as its goal local control, or (2) brain tumors are diffuse, which is to say that the cells rapidly grow beyond their initial locus, and our research goal is the prevention or treatment of the advancing tumor front. Clearly both hypotheses have merit and, in fact, almost certainly, both are true. The question becomes, should we devote our research energies to one hypothesis at the exclusion of the other?

The notion that brain tumors are local is supported by a number of observations. Most malignant gliomas present as single masses. When tumors recur after treatment, they generally do so adjacent to their original site. As pointed out by Hochberg and Pruitt, 80% of patients' tumors recur within the 2-cm edge of the original tumor's site, a finding confirmed by Albert et al using magnetic resonance imaging studies showing tumors growing out from the initial local site.

**BRAIN TUMORS AS LOCAL DISEASE**

Much of our treatment has been based on the need to achieve control of local disease before attempting to treat tumor cells beyond that 2-cm margin of the original tumor. Indeed, most successful treatments are based on this notion. Surgery has improved enormously with the advent of lasers, and, more recently, computer-assisted navigation aides, such as the ISG Wand, now make it possible to do precise resections in patients with malignant glioma. As Berger et al have pointed out, surgery is probably still the best mode of therapy for patients with lower-grade glioma. While there is ongoing debate about the role of surgery in the treatment of malignant brain tumors, my view is that surgical resection is very much a part of brain tumor therapy in that it kills the tumor and removes it at the same time. Surgery allows us to better define the grade of the tumor and permits patients to return to functionally active lives while we are treating with radiation and chemotherapy. In our study from the Brain Tumor Cooperative Group, resection of tumors to small volumes as measured on computed tomography was associated with statistically prolonged survival. This was not related to the volume of resection, but rather to the amount of residual tumor. Clearly, if most of the tumor can be removed, patients live longer. Surgical treatment as an approach to local tumor can be highly effective.

With respect to radiation therapy, we have gone from whole brain radiation therapy 30 years ago to conformal radiotherapy techniques, all in an effort to treat local disease. Early on, it was demonstrated that patients treated with cone-down boost radiation therapy lived as long as those treated with whole brain radia-
tion therapy. Now we believe that radiation can be entirely local. For example, iodine 125 seeds may be accurately placed using stereotactic techniques. We studied the effect of interstitial iodine 125 implants added to localized external beam radiation therapy—delivered to the enhanced tumor with a 2-cm margin—for a total of 120 Gy to the tumor. Patients lived a bit longer with this combined treatment. Radiosurgery is now being tested in the same manner. In centers so equipped, the peacock system uses conformal radiation therapy, reducing radiation to the surrounding brain. This system is best suited for low-grade gliomas, but does highlight local radiation therapy.

Even chemotherapy, which is really designed for the hypothesis that brain tumors are diffuse, has become local with the advent of chemotherapy-impregnated polymer wafers. The study by Brem et al demonstrated that carmustine (1,3-bis[2-chloroethyl]-1-nitrosourea) could be delivered with modest effectiveness to patients with recurrent gliomas.

Perhaps in no other way has the notion that brain tumors are local been more accepted than in the early experiments with gene therapy. Retroviral vectors (mouse fibroblasts) have been used to transfer HSV-tk into mammalian tumor cells. The HSV-tk is incorporated into the mammalian cell, which then is able to convert ganciclovir to its activated triphosphate form and becomes toxic to the cell. The process requires a bystander effect to kill cells not infected with vector. A series of investigations from the National Institutes of Health demonstrated the value of HSV-tk plus ganciclovir in rat tumors in the laboratory. These studies have been extended to a clinical trial. Fifteen patients with recurrent malignant brain tumors were treated using intratumoral implantation of murine cells that had been genetically modified to release retroviral vector containing the HSV-tk retroviral vector, following which the patients were treated with systemic ganciclovir. Responses (tumor shrinkage) occurred in several small tumors, but not the larger ones. This study, representing an early clinical attempt to use gene therapy, nicely highlights many of the problems that still need to be solved. Despite the theory that the retrovirus should have entered tumor cells, little HSV-tk RNA was demonstrated in situ in tumor cells (but was present in endothelial cells) and there was limited gene transfer in solid tissue, no penetration of vector particles into intercellular spaces, and a major reliance on the bystander effect.

Using a similar local approach, Laske et al described regional therapy of recurrent malignant brain tumors with transferrin-CRM107, a conjugate of human transferrin (Tf) and a genetic mutant of diphtheria toxin (CRM107) that lacks native toxin binding. The material was administered using high-flow interstitial microinfusion. By magnetic resonance imaging evaluation, responses occurred in 9 of 15 evaluable patients, including 2 complete responses. Transferrin receptors are highly expressed on rapidly dividing cells, including glioblastoma multiforme and other tumors. The toxin depends on transferrin to get it into cells by binding the transferrin receptor, which is internalized by endocytosis. The conjugate must be delivered locally and, because of size (140 kd), cannot cross the blood-brain barrier—hence, the use of high-flow interstitial microinfusion.

These examples demonstrate how we have focused much of our research efforts on brain tumors as local disease.

### BRAIN TUMORS AS DIFFUSE DISEASE

Let us now turn to the second hypothesis, which states that brain tumors, especially malignant gliomas, are not local, but in fact early in their history grow in a diffuse manner. Studies by Burger demonstrated the widespread occurrence of isolated tumor cells that have developed, or continue to use, powers of motility to invade the surrounding brain. The notion that tumors are already widespread at presentation was supported by the observation that even if hemispherectomies were performed to treat brain tumors, patients ultimately died of tumor at a distance. It is clear that if rapid diffuse growth occurs in brain tumors, local therapies are ultimately destined to fail.

Actually, early treatments assumed brain tumors to be diffuse although we focused our research toward local therapies as their technologies improved. Radiation therapy was originally delivered to the whole brain, but later was restricted to the tumor bed. The whole notion of chemotherapy given systemically was based on the idea of treating both residual tumor cells left locally after initial surgery and tumor cells that had already moved away from the primary site. As shown by the Brain Tumor Cooperative Group studies, chemotherapy does work, at least to some degree, suggesting either that we are blocking progressive local growth or that we are able in some cases to kill tumor cells at a distance. Anaplastic astrocytomas are more sensitive than glioblastomas, and oligodendrogliomas may be particularly chemosensitive.

Will the future of experimental treatments permit us to treat tumor cells at a distance? Empirical testing of several chemotherapy schemes is ongoing, including temozolomide, intra-arterial cisplatin plus oral etoposide, tamoxifen alone and in combinations, paclitaxel, 9-aminocamptothecan, and topotecan. Nonchemotherapy treatments include targeting growing blood vessels with TNP-470 and similar agents, growth factor signal transduction inhibitors like SU-101, monoclonal antibodies, and advanced forms of gene therapy. Can we specifically target tumor cells no matter where in the brain they reside? This was the aim of monoclonal treatment, an aim that has yet to achieve success but may be helped by the discovery of specific molecular biologic abnormalities, eg, differences in p53, the newly discovered PTEN/MMAC1 gene, or variations in epidermal growth factor or platelet-derived growth factor and the specific cell cycle checkpoints that are increasingly being defined.

### TUMOR CELL HETEROGENEITY

One problem inherent in all brain tumor research is that gliomas are heterogeneous. Work by Shapiro et al proved that individual human brain tumors were highly heterogeneous within themselves, and that different patients’ tumors with the same diagnosis differed considerably one
from another. This genetic heterogeneity was not only evident in the chromosomal patterns but also extended to the phenotypic behavior of the cells within the tumors, especially intrinsic or acquired resistance to treatment. The treatment that they studied in greatest detail was chemotherapy, and specifically chemotherapy with carmustine. However, the same observations have been made with cisplatin and radiation therapy. Without treatment, the tumor’s basic cellular instability tends to perpetuate heterogeneity. During cell division, the near-diploid tumor cell undergoes new structural or numerical chromosomal changes generated by several endopolyploidy mechanisms. Thus, tumors change their chromosome number (DNA content) with time, most commonly to become near-triploid or near-tetraploid in modal chromosome number. However, when tested, these near-triploid and near-tetraploid cells are often more sensitive to irradiation and chemotherapy than is the near-diploid cell generating the cellular diversity. These experiments have demonstrated that a relatively homogeneous group of tumor cells may be selected by increasing doses of carmustine chemotherapy. Similar selection occurs in patients. In paired initial and recurrent operative studies from the same patients undergoing treatment with radiation and chemotherapy, it was found that the cell populations at the time of recurrence were much more homogeneous than at initial resection, and were resistant to the chemotherapeutic agents used to treat the patient. If nothing further is done, these cells again evolve toward heterogeneity.

What can be inferred from these observations about how to make treatments better? They suggest that we might take advantage of the change toward homogeneity produced by treatment so as to focus efforts on cells that are more alike than not alike, ie, more homogeneous in their characteristics, even as they become more resistant to a specific form of treatment. At least a larger proportion of tumor cells will share the same genetic characteristics at this stage than when they were so heterogeneous at the patient’s presentation. Finding an appropriate therapeutic target in these cells is likely to be more successful because the target may be present in more of the tumor cells.

THE PROBLEMS OF TREATMENT DELIVERY

The next question is, to what degree must we attend to the nature of the treatments’ delivery? Ultimately all medical treatment is pharmacological, whether it is chemotherapy, impregnated wafers, or 3T3 cells containing HSV-tK vectors. We need to address the question of how to get the treatment to the brain tumor cells. Again, the problem is that focusing on treating local tumor ignores tumor cells that are growing beyond where we can inject or implant. Can we improve our treatment based on changes in pharmacology? Attempts to do so have included very high-dose chemotherapy with bone marrow rescue, intra-arterial injection of drugs, and local drug instillation using wafers. There is nothing inherently wrong in any of these techniques, but we must also deal with the associated toxicity produced by these treatments. It is true that one can rescue bone marrow and permit high doses of chemotherapy to be delivered systemically. Unfortunately, bone marrow is not the only target for drugs. Carmustine-treated patients have a greater incidence of both pulmonary and hepatic disease. Similar toxicity accompanied intra-arterial chemotherapy. Early modeling of chemotherapy delivery suggested a “first-pass” advantage for lipid-soluble drugs like carmustine if delivered intra-arterially. As shown in the Brain Tumor Cooperative Group intra-arterial carmustine trial, patients given high doses of carmustine fared worse than those given carmustine intravenously. Furthermore, intra-arterial chemotherapy produced much greater brain damage than had been anticipated by the early phase 2 studies, and ultimately we were forced to conclude that, at least for certain agents, intra-arterial chemotherapy is probably a bad idea.

Neuwelt et al have fostered the notion of forcibly opening the blood-brain barrier using hyperosmotic mannitol to treat gliomas, but to date, this has failed to produce substantial improvement in patient outcome. Furthermore, the treatment may expose the brain to toxic drugs; 50% of treatments by the technique of Neuwelt and coworkers’ result in seizures, suggesting a potentially serious limitation of choice of drugs by using this method. Recently, RMP-7, a bradykinin analog, has been demonstrated to open the barrier more in the tumor than in the brain. Trials with carboplatin with or without RMP-7 are currently underway. For all new treatments we need to attend to toxicity in the brain produced by drug delivery as well as systemic toxicity.

An important issue that is rarely addressed in brain tumor chemotherapy trials is the influence of other drugs on chemotherapy efficacy. Examples include (1) the effect of dexamethasone on closing the blood-tumor barrier, which reduces the entry of water-soluble chemotherapy agents, (2) the effect of phenobarbital on decreasing nitrosourea effectiveness, and (3) the effect of anti-epileptic drugs on chemotherapy drug metabolism. In a recently reported study of paclitaxel by Fettell and colleagues in patients with gliomas, the therapeutic results were disappointing. However, it was discovered that a standard dose of 140 mg/m² via continuous 96-hour infusion produced less than anticipated toxicity. The steady-state paclitaxel concentrations in these patients were less than 30% of those seen in patients with systemic malignancies treated at the same dose and schedule. All these patients were receiving a p450 enzyme-inducing anti-epileptic drug, usually phenytoin. The p450 hepatic enzyme system metabolizes paclitaxel. A new study was undertaken, comparing patients not receiving phenytoin with those receiving phenytoin. The maximum tolerated dose of the non-phenytoin-treated patients was 140 mg/m²; for the phenytoin-treated patients, it was 200 mg/m². Thus, phenytoin induces p450, which metabolizes paclitaxel and raises the dose requirement. It remains to be seen whether increasing the dose will improve paclitaxel efficacy in gliomas. However, the point to be made is that it is important to determine drug interactions for new agents in early studies.
PERFORMING PROPER CLINICAL TRIALS

The next issue is how to study new treatments in patients. Here again, there is a difference of opinion as to the best approaches. Many investigators believe that new treatments need to be studied extensively using phase 2 formats, and only when phase 2 studies are "positive enough" should one consider the expense of a controlled phase 3 trial. However, only phase 3 trials are definitive; even if the new treatments fail, the studies rarely need to be repeated. Reviewing 3 examples of phase 2 trials thought to be highly efficacious, one is impressed at how much time and money and especially how many patients were subjected to risk when subsequent phase 3 studies proved the treatments to be less effective, ineffective, or dangerous. The first example is intraarterial chemotherapy with carbamustine, in which the conditions of several hundred patients were touted to be improved by this technique, only to find that the technique produced severe brain damage.19 The second example is interstitial radiotherapy, which was tested initially in phase 2 studies,23 and then proven in a phase 3 trial to be less useful.6 The third example, multifractionation radiation treatment, especially for brainstem gliomas,8,22 has not yet been tested in a controlled fashion. Despite initial enthusiasm for this method, it has yet to be proven better than single-fraction radiation therapy, and indeed is probably not any better.

It might be better to consider controlled trials earlier rather than later. I think we should determine appropriate treatment doses and their toxicities early, learn about interactions with other biologicals early, and compare new treatments with standard treatments early. And earlier, rather than later, we should investigate new treatments in a controlled fashion. It is unethical to ask patients to participate in trials for which no useful data are derived.

THE NEED TO ADD NEW TREATMENT TO CURRENT THERAPY

If we are going to introduce new modalities into tumor therapy, we must add such modalities to the treatments that we know work, even if modestly. Multimodality treatment of brain tumors was introduced in the 1970s and is still the most effective approach we have. For the future, we must not forget that the combinations of surgery, radiation therapy, and chemotherapy need to be the basic treatment modalities, and that the new modalities need to be added to these if we are going to improve outcome.

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