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NEW DELIVERY SYSTEMS FOR BRAIN TUMOR THERAPY

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Therapy of brain tumors has been limited by lack of effective methods of drug delivery. Systemic administration often fails to achieve therapeutic concentrations of drugs within intracranial tumors despite toxic systemic levels. This limitation of drug delivery results from abnormalities in the tumor microvasculature as well as restrictions imposed by the normal physiologic blood-brain barrier.

TUMOR MICROVASCULAR ARCHITECTURE

The microvasculature of solid tumors differs structurally from normal capillary beds in several important ways that restrict drug delivery to neoplastic cells. Tumor microvessels are frequently dilated, saccular, and tortuous. Their organization is highly variable from one region to another within the same tumor, and microvascular branching patterns are often abnormal. Architectural features such as arteriovenous shunts or anastomoses between venules may also contribute to highly variable patterns of blood flow within solid tumors.[34,35,41] Interstitial pressures are elevated and microvascular pressures are abnormally low, so that many of the tumor microvessels may be partially or completely collapsed.[33,34] These factors contribute to diminished blood flow measured in brain tumor vessels compared with that in adjacent normal pial vessels and limit the tissue penetration of pharmacologic agents from the bloodstream to the tumor parenchyma.[81]

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THE BLOOD-BRAIN BARRIER

The tight junctions of the cerebral capillary endothelium, which form the anatomic basis for the blood-brain barrier, restrict the influx of molecules from the bloodstream into the brain. Although the blood-brain barrier is critical for homeostatic control of the biochemical milieu of the central nervous system, it also restricts access of many potentially beneficial therapeutic agents to the brain parenchyma. Attempts to improve drug delivery by biochemical or osmotic modification of the barrier[1,15,26,29-31,50] or by modification of pharmacological agents to make them more lipophilic have been moderately successful;[55] however, these strategies have not yet significantly increased the number of drugs available for treatment of brain tumors.

NEW DELIVERY METHODS

Conventional strategies for improving intravenous drug delivery to brain tumors usually require increasing the dose, frequency, or duration of drug administration. High systemic drug levels are often required to achieve adequate drug concentrations within the central nervous system. This approach is usually limited by systemic toxicity. A variety of alternative techniques have been designed to improve drug delivery to brain tumors and limit systemic toxicity by reducing the volume of distribution of the drug. These techniques include intra-arterial, intrathecal, intraventricular, and interstitial drug administration.[64]

Intra-arterial Therapy

Catheterization of the carotid or vertebral arteries for intra-arterial administration of chemotherapeutic agents such as the nitrosoureas has been used to permit more selective drug delivery to brain tumors. In rat brain tumor models, this technique was shown to permit higher drug concentrations in the brain on the side of the infusion than is possible with intravenous drug delivery.[78] This permitted the use of significantly lower doses than were necessary for equivalent therapeutic effects using intravenous injections.[13]

Unfortunately, the therapeutic promise of intra-arterial drug delivery has not been supported by clinical trials in patients with metastatic[44] or primary brain tumors.[38,60,62,76] In these studies, complications associated with intra-arterial therapy included transient orbital or head pain, periorbital and scleral erythema, retinal toxicity and blindness, and significant leukoencephalopathy. In a phase III study, survival rates in patients treated with intra-arterial carmustine (BCNU) injections were unchanged or worse than those for patients treated with conventional intravenous therapy. Thus, it was concluded that intra-arterial therapy with BCNU is neither safe nor effective.[60] The toxicity and lack of efficacy of intra-arterial therapy may be related to inhomogeneous mixing of the infused drug in the arterial bloodstream, a phenomenon known as "streaming" that has been demonstrated in vitro and in vivo.[2,16,43] The use of infusion techniques that minimize streaming may be of clinical value in the future and warrant further investigation.

Intraventricular and Intrathecal Therapy

Injection of drugs into the lumbar thecal sac, the cerebral ventricles, or the basal cisterns of the brain has been an important method of treatment for patients

with malignancies affecting the cerebrospinal fluid (CSF) spaces or adjacent surfaces of the brain and spinal cord. The CSF-brain barrier, however, prevents significant drug penetration from the CSF spaces into the brain parenchyma; consequently, intrathecal and intraventricular drug infusions have been of limited benefit for treatment of intraparenchymal brain tumors.[64]

In appropriately selected patients, lumbar puncture for intrathecal administration of antineoplastic agents has been safely used for treatment of carcinomatous or leukemic meningitis.[37]

The Ommaya reservoir, introduced in 1963,[54] has facilitated the use of intermittent bolus injections of drug into the ventricular CSF, a process that previously required an externalized catheter or repeated direct needle punctures of the lateral ventricles through a frontal burr hole. More recently, continuous sustained intraventricular or intrathecal drug infusions have been made possible by a variety of implantable mechanical or electronic pumps.[27,45,57]

Interstitial Therapy

The most direct method of by-passing the barriers to drug delivery imposed by the abnormal tumor microvasculature, elevated interstitial pressure, and the normal brain capillary endothelial tight junctions is to administer therapeutic agents directly into the tumor parenchyma. Theroretically, interstitial therapy should maximize drug delivery to the tumor while minimizing systemic toxicity. With this approach to drug delivery, interstitial pressure gradients and drug concentration gradients favor drug redistribution from the center to the periphery of the tumor by a combination of convection and diffusion.[34] Interstitial drug delivery is particularly appealing for the treatment of primary brain tumors such as the malignant gliomas because these tumors generally recur locally and systemic metastases are exceedingly rare.[28] Approaches to local drug delivery include the use of implantable catheters and implantable controlled-release polymer systems.

Catheter and Pump Systems

Soon after its introduction, the Ommaya reservoir was first used to treat malignant gliomas with methotrexate.[59] Since that time, catheters with or without pump systems have been used to administer methotrexate,[23,51,75] nitrosoureas,[79] bleomycin,[4,48] adriamycin,[32] cisplatin,[5,] and lymphokine-activated killer cells[49] directly into tumor parenchyma or resection cavities.

Although these studies demonstrate that intratumoral infusion is feasible and may be well tolerated, this has not been proven more effective than less-invasive methods of treatment. The major risks of CNS infusion techniques include infection, catheter obstruction, and neurotoxicity. Intermittent drug infusions may also be limited by the failure to generate an adequate sustained concentration gradient to promote drug penetration into the tumor parenchyma.[42] To overcome this drug penetration problem, Bouvier and coworkers[5] reported the implantation of 68 catheters for the delivery of cisplatin into the brain of a patient with a malignant glioma. Although this system halted progression of the disease, the tumor recurred and the patient died 6 months after therapy.[5] Another strategy for improving drug penetration through tumor and brain parenchyma by using continuous drug infusions to maintain pressure gradients favoring drug convection is being developed and tested at the National Institutes of Health.[3]

Polymer Systems

A variety of biocompatible controlled release polymers have been developed as alternative systems for interstitial drug delivery. These devices are available in biodegradable and nonbiodegradable forms.

The best example of a nonbiodegradable controlled release polymer is the ethylene-vinyl acetate copolymer (EVAc), a biologically inert polymer that releases incorporated drugs by simple diffusion. Although this system has been studied extensively and is used clinically, it has not yet been approved for clinical investigation as a drug delivery device for the brain. The primary limitation of EVAc and other nonbiodegradable controlled release polymers is that they remain as foreign bodies in the brain long after drug release has ceased. Nevertheless, EVAc has proven invaluable as a research tool permitting proof of the principle that use of controlled release polymers for interstitial drug delivery is feasible, well-tolerated, and effective against experimental brain tumors. Because it is easy to work with, EVAc has also been useful in the laboratory as a screening tool to test new pharmacological agents for safety and efficacy against animal brain tumor models.

Biodegradable polymers such as the polyanhydrides release drugs by a combination of drug diffusion and polymer degradation. Because these polymers degrade completely in the presence of water, they do not remain in vivo as foreign bodies but rather are hydrolyzed to yield their component monomers. These degradation products are noncytotoxic, nonmutagenic, and nonteratogenic.[40]

Two polyanhydride polymer systems have been studied extensively as vehicles for interstitial drug delivery in the brain. The first of these devices is poly[bis(*p*-carboxyphenoxy) propane-sebacic acid] or *p*(CPP-SA). Incorporation of drugs into this polymer is a simple process that is performed at room temperature. The polymer can be manufactured in a variety of physical forms, such as sheets, rods, microspheres, nanospheres, or wafers and may therefore be implanted by a variety of surgical techniques, including stereotaxy. By modifying the ratio of CPP to sebacic acid (SA), the polymer degradation time can be adjusted according to the desired period of drug release. *p*(CPP-SA) is particularly well-suited for delivery of hydrophobic compounds. In preclinical animal studies and human clinical trials, it has been demonstrated to be biocompatible and safe for use in the brain.[7-10,65]

A second polyanhydride polymer, fatty acid dimer-sebacic acid (FAD-SA), shares many of the advantages listed for *p*(CPP-SA) but was designed to optimize interstitial delivery of hydrophilic and hydrolytically unstable compounds such as methotrexate, carboplatin, and 4-hydroperoxycyclophosphamide (4-HC).[17] This device has also been extensively tested in animal models[6,12] and appears to be a promising candidate for human clinical trials.

POLYMER-MEDIATED INTERSTITIAL DELIVERY OF BCNU

The nitrosoureas are a class of alkylating agents that are highly lipid-soluble and essentially nonionized; therefore, they cross the blood-brain barrier and have often been used for the treatment of brain tumors. The single most commonly used and most-effective chemotherapeutic agent for brain tumors has been BCNU. Systemic administration of this drug has provided modest improvements in patient survival, but its efficacy has been limited by myelosuppression, hepatic toxicity, and pulmonary fibrosis.[39]

Because delivery of BCNU directly into the parenchyma of brain tumors could result in very high local drug concentrations while by-passing the systemic circulation, it was postulated that interstitial BCNU therapy via implantable polymers

would maximize this drug's proven efficacy by eliminating or minimizing the constraints imposed by its systemic toxicity. This hypothesis has been rigorously tested in a series of preclinical investigations and clinical trials.

Once the biocompatibility of EVAc and *p*(CPP-SA) was established,[8,65] BCNU was incorporated into these polymers and the distribution and pharmacokinetics of active drug release were determined in vitro and in vivo. These studies demonstrated that controlled, sustained release of intact BCNU is possible by use of these polymer systems, and that high local concentrations of the drug in brain tissue can be achieved with these implants.[25,77,80] Subsequent preclinical studies have shown that interstitial delivery of BCNU from polymers is well-tolerated in the brains of rodents[67] and primates[11] and that concomitant radiation therapy did not lead to any adverse effects.[11] These implants effectively reduce the rate of tumor growth and prolong survival in the rat 9L-gliosarcoma model.[67]

On the basis of the preclinical studies, phase I-II clinical trials of the effect of interstitial BCNU incorporated into the *p*(CPP-SA) polymer were conducted in 21 patients with recurrent malignant gliomas. In these patients, up to eight polymer wafers containing BCNU were implanted into the surgical resection cavity at the time of tumor debulking (Fig. 1 through 3). Three increasing doses of BCNU were studied and all were found to be well-tolerated and safe in the brain.[9]

A phase III randomized, double-blind, placebo-controlled clinical trial of *p*(CPP-SA) containing 3.8% BCNU by weight was conducted at 27 medical centers in 222 patients with recurrent malignant gliomas. In this study, the BCNU-containing polymers significantly prolonged patient survival. Furthermore, in marked contrast to the many toxic effects commonly experienced by patients treated with systemic or intraarterial BCNU therapy, no significant adverse effects were associated with these implants.[10]

On the basis of the safety and significant efficacy demonstrated in the clinical trials of 3.8% BCNU in *p*(CPPA-SA), future studies to evaluate higher doses of BCNU in the polymer are planned. The role of these polymers as part of the initial treatment of gliomas is also being evaluated.

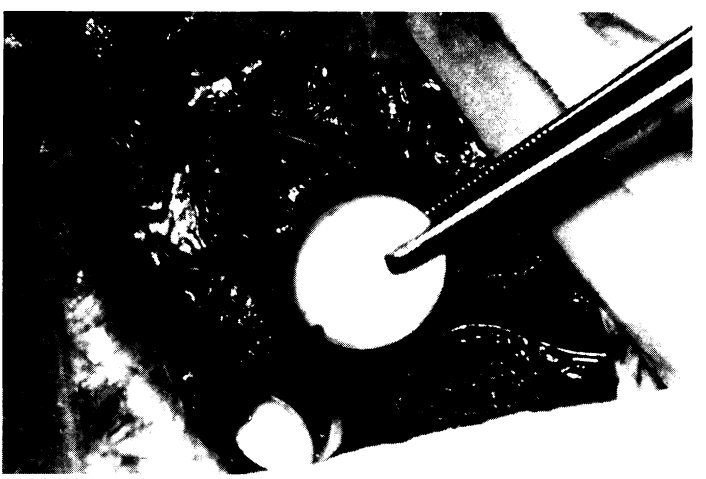

Figure 1. A dime-sized polyanhydride polymer disc containing BCNU is inserted into the surgical resection cavity after removal of a malignant glioma.

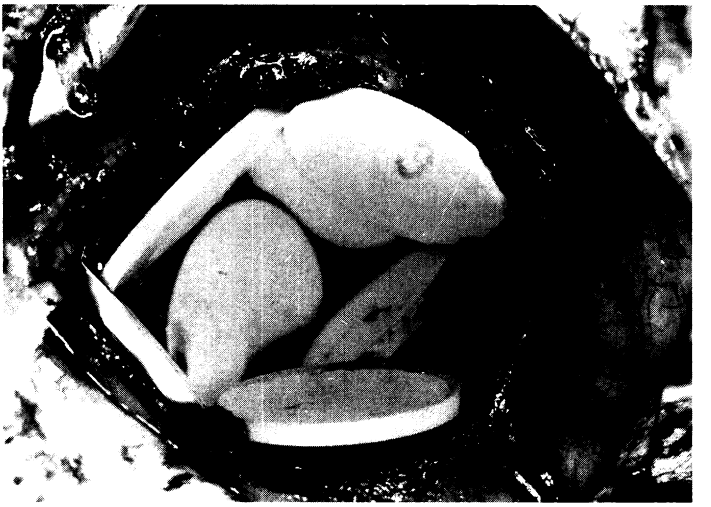

Figure 2. After completion of surgical resection of a malignant glioma, the walls of the tumor cavity are seen lined with polymer discs containing BCNU.

OTHER DRUG-POLYMER COMBINATIONS

The safety and efficacy with which the polyanhydride polymer permits intracranial BCNU administration suggest that this drug delivery method could be used for a wide array of therapeutic agents that have not previously been successfully used for treatment of brain tumors or other central nervous system diseases.

Figure 3. Nonenhanced T1-weighted MR imaging of a patient after resection of a malignant glioma and implantation of polymers containing BCNU. The polymer discs appear as linear low signal intensity objects on this imaging sequence (*arrows*).

Chemotherapeutic Drugs

A variety of other chemotherapeutic agents, including 4-HC,[12,36] carboplatin,[52,53] camptothecin (National Cancer Institute, Bethesda, MD),[73] and paclitaxel (Taxol)[72] have been safely delivered intracranially in implantable polymers and effectively improve treatment of brain tumors in rats. 4-HC is a hydrophilic derivative of cyclophosphamide that does not cross the blood-brain barrier. Unlike its parent compound, 4-HC is appropriate for intracranial delivery because it does not require hepatic activation. Carboplatin is a derivative of cisplatin that was selected for intracranial use because of reduced neurotoxicity and adverse systemic effects compared with its parent compound.[53] Camptothecin is a naturally occurring inhibitor of topoisomerase I that has potent antitumor effects in vitro. Unexpected toxicity and lack of efficacy against melanoma[24] and gastrointestinal carcinoma[47] in early clinical trials, however, have prevented systemic use of this drug in patients with malignant brain tumors and justify consideration of local delivery. Paclitaxel (Taxol) is a microtubule binding agent with demonstrated clinical efficacy against breast, ovarian, and non-small cell lung carcinoma.[58] Because it is effective in vitro against glioma cell lines[14] but does not cross the blood-brain barrier, paclitaxel (Taxol) is another promising agent for use interstitially.

Each of these agents prolongs survival in rodent brain tumor models when implanted interstitially using biodegradable polymers.[12,36,52,53,72,73] Preclinical safety and drug distribution studies are underway in primates in preparation for possible clinical trials.

Anticonvulsants

The use of phenytoin as an anticonvulsant is associated with a variety of adverse systemic effects, including cutaneous rashes, hepatitis, and megaloblastic anemia. Because more than 90% of the circulating drug is bound to plasma proteins, it crosses the blood-brain barrier poorly. Because of fluctuating hepatic clearance and erratic drug absorption, it is often difficult to maintain proper therapeutic drug levels in plasma. For these reasons, phenytoin is a good candidate for local drug delivery in patients who undergo craniotomy.

Chronic seizure disorders in rats may be produced by applying cobalt chloride to the cerebral cortex. In this model, interstitial delivery of phenytoin safely and effectively reduced the incidence of seizures as measured by the overall EEG grade, the total number of seizure spikes on the EEG, and the Racine behavioral scale. The polymers released phenytoin in a sustained fashion with no apparent behavioral toxicity over the course of 11 months.[68]

Steroids for Vasogenic Edema

Administration of high systemic doses of corticosteroids is widely used to control the vasogenic edema associated with brain tumors. The prolonged use of therapeutic doses of steroids, however, is associated with serious adverse effects, including hemorrhagic gastric ulcers, atrophic skin changes, diabetes, myopathy, and osteoporosis.[46] It was hypothesized that interstitial delivery of dexamethasone would more safely control peritumoral edema. To test this hypothesis, in vitro and in vivo pharmacokinetic studies of dexamethasone release from polymer implants were first conducted. These studies demonstrated that, in contrast to systemic injections, interstitial therapy resulted in higher steroid concentrations in the brain and

lower concentrations in plasma.[56] Comparable results were obtained in tumor-bearing rats:[69] controlled-release polymers deliver biologically active dexamethasone in a sustained fashion and vasogenic edema is effectively reduced by using these implants in the rat 9L-gliosarcoma model.[69]

Inhibitors of Tumor Angiogenesis

The growth of solid tumors in the brain, as in other locations throughout the body, is dependent on the ability of neoplastic cells to induce new vessel growth from the host vasculature, a process known as tumor angiogenesis.[21] By inhibiting vascular proliferation, it is therefore possible to modulate the growth of these neoplasms.[18-20]

Cortisone, when administered in combination with heparin, has potent antiangiogenic effects.[22] This property is preserved when heparin and cortisone are loaded into polymers for interstitial delivery, and when implanted into rat 9L-gliosarcoma, the polymers inhibit tumor growth.[66] These experiments established that polymer-mediated interstitial antiangiogenic therapy is feasible and effective in controlling tumor growth.

Minocycline, a semisynthetic derivative of tetracycline, is another agent that has been shown to inhibit tumor angiogenesis.[63] When delivered systemically, minocycline effectively prolongs the survival of mice with subcutaneously implanted Lewis lung carcinoma.[61,70,71] For efficacy against established intracranial tumors in the rat 9L-gliosarcoma, however, minocycline must be delivered interstitially.[74] This effect is potentiated by the concurrent administration of systemic BCNU.[74]

FUTURE APPLICATIONS

As with other malignant neoplasms, a human glioma is a heterogeneous population of cells that is diffusely infiltrative and tends to recur locally. No single therapeutic approach is likely to be curative in the foreseeable future. Instead, the most successful strategies will use rational combinations of synergistic or complementary treatment modalities. Drug delivery polymers are particularly important because they permit treatment of brain tumors and other central nervous system pathology with a diverse array of agents that previously could not be efficiently, safely, or effectively delivered to the brain. This new route of administration will allow use of combinations of new and established chemotherapeutic agents along with modulators of drug resistance, antiangiogenic agents, cytokines, immunotoxins, anticonvulsants, or inhibitors of vasogenic edema. Interstitial chemotherapy may soon be used to enhance the efficacy of systemically administered drugs by locally disrupting the blood-brain barrier. Radiosensitizing agents, implanted locally at the time of tumor resection, could potentiate the antineoplastic effects of postoperative external beam irradiation.

We anticipate that in the future, patients with brain tumors will first undergo biopsy. The tumor specimen will then be studied in the laboratory to characterize the lesion fully, including its patterns of drug resistance. At the time of tumor resection, the specific best therapeutic combinations for that patient's tumor will be administered by polymer implantation. Adjuvant therapy will be administered postoperatively. If the tumor recurs, the same cycle of diagnostic and therapeutic interventions will be repeated. The new biopsy sample will be studied to determine whether the tumor has acquired new patterns of drug resistance since it was first characterized. This will permit selection of the optimal interstitial agents for treatment of the recurrence. With the use of this treatment approach (Fig. 4), im-

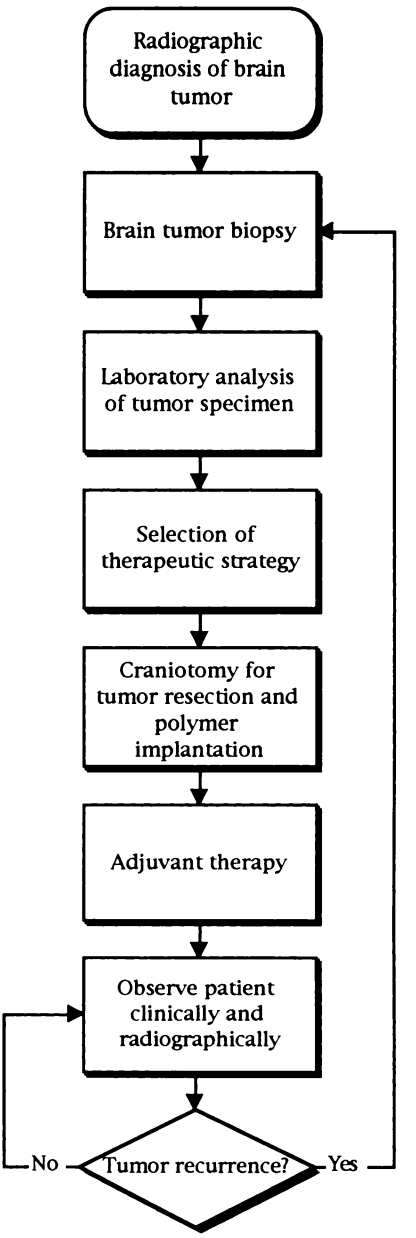

Figure 4. Proposed future clinical approach to management of patients with malignant brain tumors.

plantable polymer drug delivery systems will permit highly individualized therapy for patients with malignant brain tumors.

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