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Intratumoral Chemotherapy

Walter Kevin A. M.D.; Tamargo, Rafael J. M.D.; Olivi, Alessandro M.D.; Burger, Peter C. M.D.; Brem, Henry M.D.

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Abstract

IN AN EFFORT to improve survival from malignant gliomas, investigators have used intratumoral chemotherapy protocols to deliver high doses of tumoricidal agents directly to the brain. Theoretically, these infusions bypass the blood-brain barrier, minimize systemic drug levels and the side effects of chemotherapy, and achieve prolonged elevations of intracerebral chemotherapeutic agents relative to those obtainable by systemic administration. Almost all major classes of chemotherapeutic agents have been examined as possible intratumoral therapies via delivery approaches ranging from simple intratumoral injections to implantable computer-driven constant infusion pumps and biodegradable polymer matrices. In this review, we summarize the major clinical trials and experimental investigations underlying the development of intratumoral chemotherapy as a treatment for gliomas.

The prognosis for patients with malignant gliomas has remained dismal despite significant advances in neurosurgery, neuroradiology, radiotherapy, and chemotherapy. The median survival for patients with glioblastomas is still less than 1 year after diagnosis and treatment with surgical resection, external beam radiation therapy, and systemic chemotherapy. An experimental approach for improving the outlook for patients with gliomas has centered on eradicating residual tumor cells surrounding the site of an original tumor. These efforts stem from clinical observations that 90% of malignant gliomas recur within 2 cm of an original resection site and that metastases outside of the central nervous system (CNS) from gliomas are rare (45). Local control of a glioma can potentially prevent or delay tumor recurrence and prolong survival from the disease. Interstitial radiation and

radiosurgery have had some success in local control of glial tumors (58), but local chemotherapy that is more selective and less neurotoxic than these techniques is desired (111). The methods for administering intratumoral chemotherapy have ranged from a simple intratumoral injection through an indwelling catheter to the use of controlled delivery systems, such as programmable subcutaneous pumps and biodegradable polymer matrices. Almost all major classes of chemotherapeutic drugs have been tested in conjunction with these devices. The objective of this review is to consolidate and evaluate the clinical and experimental experience to date with intratumoral chemotherapy as a means of treating gliomas.

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RATIONALE FOR INTRATUMORAL CHEMOTHERAPY

Malignant gliomas have largely been refractory to treatment with systemic chemotherapy. Although two large Phase III clinical trials have validated the role of chemotherapy in treating glioblastomas, the increases in patient survival have been modest (33,118). There are two approaches to improve the responsiveness of gliomas to chemotherapy. The first approach focuses on developing newer agents with novel mechanisms of action that may have additional antitumor activity. Alternately, the second approach may maximize the effectiveness of current chemotherapeutic agents by altering their pharmacodynamic and pharmacokinetic properties such that their biodistribution and availability are optimized for antiglioma activity. Intratumoral chemotherapy focuses largely on this second approach by increasing drug concentration at the tumor target, by reducing the systemic exposure and toxicities of chemotherapeutic agents, and by lengthening the duration of exposure of the tumor to the drug.

By virtue of their anatomic location, gliomas are at least partially shielded from systemic chemotherapeutic agents by the blood-brain barrier. This barrier is mostly impenetrable to agents that are high in molecular weight or hydrophilic or that possess an ionic charge (35). Thus, systemic chemotherapy protocols may be unable to deliver tumoricidal drug concentrations to the tumor target without incurring unacceptable systemic side effects. Delivering chemotherapeutic agents directly to the tumor bed

bypasses the blood-brain barrier and improves drug concentration at the target compared with that which may be obtained by systemic delivery.

Although the blood-brain barrier is largely disrupted within the tumor core (3,13,116,117), allowing some systemic chemotherapeutic agents access to the tumor, the barrier is mostly intact at the growing tumor margin. Microscopic foci of malignant cells at the tumor margin may be protected by the blood-brain barrier and be responsible for disease relapse after surgical resection or radiotherapy to the tumor core. Clinical studies have confirmed that although therapeutic levels are attained for diverse chemotherapeutic agents (e.g., etoposide, teniposide mitoxantrone, and bleomycin) within a necrotic tumor, drug levels are markedly lower or nondetectable in the peritumoral region (27,41) and that the permeability of the blood-brain barrier rapidly decreases at the tumor margin (1,61). Furthermore, in clinical (38,76) and animal (46) studies, investigators have reported improved survival in patients with malignant gliomas with the administration of systemic chemotherapy after using hyperosmotic or chemical agents to disrupt the blood-brain barrier. Thus, developing strategies, such as intratumoral drug delivery to bypass the blood-brain barrier, seem to be useful approaches for treating patients and valuable methods of optimizing the antitumor activity of existing agents.

Intratumoral chemotherapy minimizes the systemic exposure to drugs. All chemotherapy compounds have significant dose-limiting toxicities, such as bone marrow suppression, stomatitis, nausea, and vomiting. In a sense, these side effects are caused by "wasted" drug, the effect of which is being exerted at a site other than the desired target. Intratumoral chemotherapy delivers the drug directly to the target, reducing the side effects caused by systemic exposure. Thus, intratumoral chemotherapy may improve the quality of life for patients receiving therapy.

Intratumoral administration can be accomplished using sustained-release or constant-infusion technology to maintain elevated drug concentrations within the tumor for extended periods of time. Some chemotherapeutic agents are rapidly cleared from the plasma, thereby decreasing their availability for exchange into the intracerebral compartment. Carmustine (BCNU), for example, has a serum half-life of <15 minutes (64). By the use of sustained-

release technology, however, tumoricidal concentrations of BCNU can be maintained intracranially for up to 21 days in animal models (36). Furthermore, certain chemotherapeutic agents exert their action in a manner specific to the cell cycle. Maintaining the intratumoral concentration of these agents for a prolonged period of time enhances the probability that replicating tumor cells will enter sensitive phases of the cell cycle during the exposure period.

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TECHNIQUES FOR ADMINISTRATION

Two distinct approaches have emerged for intratumorally delivering chemotherapy; the first involves infusing a solution via a catheter, and the second involves implanting a polymeric release matrix loaded with a drug within the tumor (Tables 1 and 2). Each of these techniques has several variations.

The simplest approach to intratumoral chemotherapy is to implant one end of a catheter within the tumor bed and leave the opposite end outside of the body. Injections can then be manually made through the catheter into the tumor bed.

An improvement over simple injections through a catheter is the use of the Ommaya reservoir, which can deliver intermittent bolus injections of chemotherapy to the tumor bed. The reservoir is implanted subcutaneously in the scalp and connected to an outlet catheter within the tumor bed. Agents can be injected percutaneously into the reservoir at various times and then delivered to the tumor by manual compression of the reservoir through the scalp. Thus, compared with an open catheter, the Ommaya reservoir reduces the risk of infection, although it does not allow for truly continuous drug delivery. The Ommaya reservoir has been extensively used for intratumoral therapy (Table 1).

Implantable pumps represent the next advance in intratumoral infusion. Like the Ommaya reservoir, pumps are subcutaneously implanted to reduce the risk of infection, but unlike the Ommaya reservoir, they can deliver a constant infusion of drugs over an extended period of time. Like the Ommaya reservoir, they also can be subcutaneously refilled. Three different pumps are currently available, each with a distinct drug delivery mechanism. Each pump type can deliver drugs at variable rates that may be externally altered from hand-held computer control units. The vapor pressure pump uses a compartment of compressed freon to deliver a solution at a constant rate (17,49). The prototype for this model is the Infusaid pump (Infusaid Corp., Norwood, MA). The MiniMed PIMS system (MiniMed, Sylmar, CA) (65) delivers drugs by a solenoid pumping mechanism. The Medtronic SynchroMed system (Medtronic, Minneapolis, MN) uses a peristaltic mechanism to deliver the infused agent (44). None of these devices has been used widely enough for intratumoral glioma therapy to permit advocating the use of one system over another.

Surgically implantable polymer matrices loaded with chemotherapeutic agents provide another approach to intratumoral drug delivery (Table 2). The matrix is loaded with the desired agent and then implanted within the tumor cavity (Fig. 1). The matrix releases its drug load over a period determined by the characteristics of the polymer. The theoretical advantage of polymer-based delivery over catheter technology is that the polymers are not subject to clogging and blockage by tissue debris. Furthermore, the polymer matrix poses a minimal burden to the patient regarding compliance. Once the polymer is implanted, it requires no maintenance or further manipulation. The major disadvantage to the matrix system is that it is not refillable, as is the pump system. If a further dose is desired, another implant must be placed surgically or injected.

Polymeric devices deliver drugs by two basic mechanisms (57). In the first, the drug diffuses from micropores in the polymer matrix. The release rate is, therefore, largely governed by the permeability of the release matrix and the diffusion properties of the drug used. In the second, the matrix itself is degraded and, thereby, releases the drug loaded within its interstices. In this case, drug release is governed by the degradation rate of the matrix.

Both release mechanisms have been clinically used. Ethylenevinyl acetate (EVAc) was described by Langer (57) in the early 1970s and is the prototype of a diffusion delivery matrix. It has found applications in glaucoma therapy with pilocarpine and as a vaginal contraceptive releasing progesterone. It has also been experimentally used to deliver drugs intratumorally for glioma therapy (106). Silicone rubber capsules (127) are also examples of diffusion-controlled devices, and they have been clinically used for intratumoral glioma therapy to deliver 5-fluorouracil (5-FU).

The polyanhydride poly[bis(carboxyphenoxy-propane)-sebacic acid] (PCPP-SA) matrix is an example of a biodegradable polymer that has been clinically investigated for glioma therapy (10). PCPP-SA has been tested for brain biocompatibility in primates (12) and nonprimates (9,60,104) and found to elicit only a minimal inflammatory reaction. Furthermore, because the matrix itself is degraded, no foreign body remains within the brain after the drug has been delivered. Its theoretical advantage over diffusion-controlled matrices is that its degradation proceeds at a constant rate (59) and is unaffected by the presence of a drug within the matrix, the pH of the extracellular fluid, or the presence of tumor in vivo (128). Thus, any drug can theoretically be incorporated into the release matrix, as long as it does not react chemically with the matrix backbone. The rate of degradation can be controlled to occur over days or years, depending on the relative ratios of the monomers in the copolymer matrix. Consequently, any desired delivery profile of a wide variety of drugs is theoretically achievable.

Recently, a second polyanhydride matrix for drug delivery to the brain has been approved for clinical trials. PCPP-SA was designed to deliver hydrophobic drugs such as BCNU. When used in conjunction with certain hydrophilic agents, however, it was found that PCPP-SA could not prevent hydrolytic degradation of the loaded agent. A second polyanhydride polymer, the fatty acid dimer-sebacic acid (FAD-SA) copolymer, was developed to address this issue. It delivers hydrophilic drugs in a more reproducible manner than does the PCPP-SA matrix. Therefore, the two polyanhydride matrices PCPP-SA and FAD-SA complement each other to optimize the delivery of hydrophobic and hydrophilic agents, respectively. Further developments may bring matrices that are tailor-made to a specific drug.

In an additional development, Menei et al. (70) have developed a poly(lactide-co-glycolide) polymer, which can be formed into microspheres and stereotactically injected into the brain. Chemotherapeutic agents can be incorporated into the microspheres during their formation. Thus, biodegradable polymers could also be used, not only as monolithic implants but also as stereotactic injections. Thus, tumors that are not amenable to surgical resection and implantation of a monolithic implant could still be accessible to intratumoral chemotherapy via stereotactic injection of poly(lactide-co-glycolide) microspheres. Currently, this approach has been investigated in rats. Gref et al. (34) have also demonstrated that poly(lactide-co-glycolide) nanospheres can be covalently linked to a polyethylene glycol shell, which reduces opsonization and elimination of the spheres by the immune system before drug release.

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INTRATUMORAL CHEMOTHERAPY: INITIAL EFFORTS

The first clinical report of intratumoral chemotherapy came from Heppner and Diemath in 1963 (43). They used a cytostatic agent, endoxan, delivered from a gelatin sponge matrix, Spongostan (Ferrosan, South Africa, and Mascia Brunelli, Italy), in 41 patients. The dose of endoxan varied between 100 and 200 mg per patient, of whom 32 had gliomas and the remaining had medulloblastomas or sarcomatous tumors. The sponge was implanted in the cavity left by the surgical resection of the tumor. The primary conclusions of the authors were that the treatment was well tolerated and full of promise, but because of the small numbers of patients and the use of intercurrent therapies, the efficacy of the treatment could not be ascertained.

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NITROSOUREAS

Nitrosoureas have been the most widely used agents for brain tumor chemotherapy. Their lipid solubility and relatively low molecular weight allow them to cross the blood-brain barrier at potentially tumoricidal concentrations (64). In a large randomized comparison of the nitrosoureas

BCNU and semustine given postoperatively with radiotherapy versus postoperative radiotherapy alone, the median survival for the chemotherapy groups was longer (BCNU and radiotherapy, 49 wk; semustine and radiotherapy, 43 wk) than that for patients receiving radiotherapy alone (37 wk) (118). Unfortunately, this result was not significant at the level of $P < 0.05$ (BCNU, $P = 0.201$; semustine, $P = 0.450$). A follow-up study, however, indicated that BCNU or procarbazine significantly improved survival compared with methylprednisone alone (33).

In an effort to improve their effectiveness, nitrosoureas have also been examined as intratumoral agents. BCNU has been delivered from polymer matrices consisting of either the polyanhydride copolymer PCPP-SA or the EVAc copolymer (Table 3) (106). Although BCNU crosses the blood-brain barrier, it is very rapidly cleared with a $t_{1/2\beta}$ of 20 minutes or less (64). BCNU also causes significant bone marrow suppression and pulmonary fibrosis, which are its dose-limiting side effects. Because local sustained delivery of BCNU potentially increases the duration of tumor exposure to the drug, as well as decreases systemic concentrations and side effects, we decided to evaluate it as an intratumoral therapy.

Extensive preclinical study with BCNU-polymer preparations demonstrated that the polymer discs were capable of releasing active BCNU for up to 21 days after intracranial implantation in the rat and rabbit brain (36,130). Studies in rabbit brain indicated that BCNU diffused widely from the polymer, with 50% of the brain exposed to BCNU with a concentration of 6 mmol/L up to 10 mm from the implant site 3 days after implantation. A comparable dose of BCNU stereotactically injected disappeared from the rabbit brain after 3 hours.

Preclinical efficacy studies of the BCNU-polymer preparation against the rat 9L glioma, both intracranially and subcutaneously, showed significant inhibition of tumor growth (106). Animals in which BCNU was delivered from the EVAc polymer had a delay in flank tumor growth by 16.3 days compared with control animals with empty polymer implants. Rats receiving the same dose of BCNU via intraperitoneal injection had a significantly shorter delay of growth (11.2 d; $P < 0.05$). A 10-mg polymer implant loaded

with 20% BCNU by weight used against an established intracranial 9L tumor significantly extended survival compared with empty polymer implants in control animals (5.4-fold and 7.3-fold for the PCPP-SA and EVAc polymers, respectively; $P < 0.05$). The survival benefit of an equivalent dose of systemically administered (i.e., intraperitoneal) BCNU was only 2.4-fold. Furthermore, when identical doses of BCNU were intracranially given to rats bearing glial tumors by polymer implant or by stereotactic intralesional injection, the polymer implant extended survival 271%, whereas the intratumoral injection only extended survival 36% compared with controls (Buahin and Brem, unpublished data). Thus, in preclinical models, the polymer implant improved survival in rats with tumors, relative to both systemically administered drugs and simple intratumoral infusion.

In preclinical toxicity studies in the monkey brain with BCNU delivered from the PCPP-SA polymer, animals that received the implant showed no evidence of neurological deficits (12). Complete blood counts performed throughout the 80-day experimental period showed no signs of systemic toxicity from BCNU. Computed tomographic (CT) scans of the implant site initially showed a radiopaque density and local cerebral edema. These postoperative changes disappeared in later scans, indicating degradation of the polymer disc in situ. Magnetic resonance imaging scans initially showed the polymer implant as a hypointense region surrounded by a ring of iso- or hyperintense material corresponding to edema or blood. These postoperative changes also resolved with time. Autopsies performed on the animals were significant for mild, localized, inflammatory reactions surrounding the implant. Brain that was distant from the polymer implant was normal. A subgroup of animals also received external beam radiotherapy in conjunction with the implant. These animals displayed only local pathological changes at the implant site.

On the basis of our preclinical data indicating that the PCPP-SA polymer discs could extend survival in rat models of malignant glioma, deliver BCNU in active form, and release the drug in a sustained fashion and were noninflammatory in the primate brain, we proceeded to Phase I clinical trials with this preparation (10). Twenty-one patients were treated with three different doses of BCNU loaded in PCPP-SA (1.93, 3.85, and 6.35% BCNU by polymer weight). The polymer was placed intraoperatively in the tumor

cavity after resection of the tumor. The overall median survival times were 46 weeks after implant and 87 weeks after initial diagnosis, with 86% of the patients alive more than 1 year after diagnosis. Frequent hematological, blood chemistry, and urinalysis tests did not reveal any systemic side effects from the BCNU-polymer preparation. Karnofsky performance scores, which measure a patient's ability to function independently, decreased slightly during the immediately postoperative period but returned to baseline within 2 weeks and were stable for 49 days. Thus, the quality of life was maintained during the chemotherapeutic period. In the course of the study, 10 patients underwent second operations for deteriorating neurological status and increased enhancement on computerized tomography or magnetic resonance imaging. At re-exploration, the most significant finding was a rim of necrotic tissue up to 1 cm deep, similar to that reported after interstitial radiotherapy. Removal of this necrotic tissue generally improved the Karnofsky score of the patient. The mean survivals for the patients were 65, 64, and 32 weeks after implant, respectively. The cause of death for each patient was tumor progression. Although there was no difference among the groups in side effects attributable to the polymer, the longer survivals in patients receiving the lower-dose polymers led to the selection of 3.85% loaded polymers for further clinical study.

A subsequent study has also been performed to evaluate the safety of the BCNU-impregnated polymer as an initial therapy for malignant glioma. In 22 patients treated with surgical resection, polymer implantation, and external beam radiotherapy, there were no clinical toxicities associated with the implant itself (8).

On the basis of these results, which indicated that the BCNU-polymer preparation is well tolerated and safe, we performed a placebo-controlled, double-blind, prospective, randomized Phase III drug trial enrolling 222 patients at 27 medical centers (11). Patients with recurrent gliomas were randomized to have either a polymer loaded with 3.85% BCNU or an empty placebo polymer implanted on the surface of the resected tumor cavity. The surgeons were unable to determine whether the polymer contained active drug at the time of implantation. Randomization balanced the treatment and control groups in prognostic variables. Two weeks after polymer implantation, patients were allowed to begin systemic chemotherapy and

were radiologically and clinically assessed every 2 months. Decisions about additional tumor resections were made by the patient's surgeon, independent from the study. Before the study, all of the patients in each group had undergone radiotherapy, and 52.7% of the BCNU-polymer group and 48.2% of the control group had undergone previous chemotherapy. Within 6 months of the polymer implantation, 11.8% of the BCNU-polymer group and 11.6% of the control group underwent second operations. Additionally, within this 6-month period, 25.5% of the BCNU-polymer group received additional systemic chemotherapy compared with 18.8% of the control group. None of these differences between the treatment and control arms of the study reached statistical significance.

The BCNU-polymer treatment group had a median survival of 31 weeks compared with the empty polymer group, whose median survival was 23 weeks. When these results were analyzed using a Cox proportional hazards regression model, which takes into account such variables as tumor grade and patient age between groups, the hazard ratio was 0.67 ($P = 0.007$). Furthermore, for the 73% of the patients enrolled in the study who had tumors that were histologically consistent with glioblastoma multiforme, the BCNU-polymer improved the 6-month survival by 50% ($P = 0.02$). The side effects from the BCNU-polymer preparation were minimal, with no significant incidence of the toxicities usually associated with systemic BCNU therapy, such as anemia or thrombocytopenia. There was no increase in the incidence of CNS toxicity associated with the implant beyond what would be expected for patients undergoing a repeat craniotomy (25), except for a slight increase in the incidence of local infection associated with the polymer implant, which was not clinically significant (BCNU-polymer group 3.6%; control group, 0.9%). Postmortem examination of the patients receiving BCNU-loaded and empty polymer discs revealed a small band of coagulation necrosis surrounding the implant. There was also fibrous membrane in the tumor beds of several patients. These findings were less marked in the patients receiving empty implants than in those receiving BCNU-loaded polymer discs. There was also a slight granulomatous inflammatory response in the tumor beds of patients receiving the BCNU-loaded polymer. In no patient was there extensive necrosis surrounding the implant, however. These results indicate that BCNU-impregnated polymers are safe and can modestly prolong patient survival in patients who have been heavily pretreated before

enrollment in the trial. Further studies will seek to evaluate higher doses in BCNU-loaded polymers as well as address the therapy as an initial treatment for brain tumors.

Other laboratory investigations have also examined a variety of polymers to deliver nitrosoureas. Rosenblum et al. (93) demonstrated that silicone rubber capsules could release 1-(2-chloroethyl)-3-(*trans*-4-methylcyclohexyl)-1-nitrosourea at a constant rate for up to 30 days in vitro, despite the hydrophobicity of this compound and its instability in aqueous solution. When the 1-(2-chloroethyl)-3-(*trans*-4-methylcyclohexyl)-1-nitrosourea capsules were placed in the rat flank, the amount of drug released increased by 50 to 60%.

Refojo et al. (89), Liu et al. (63), and Ueno et al. (113) have also reported on the release of BCNU from silicone rubber capsules and proposed this formulation as a treatment for intraocular malignancies. The rate of BCNU release from the device was proportional to the surface area and surface thickness of the silicone capsule and to the amount of BCNU loaded in the capsule. One proposed advantage of the silicone capsules is that they could be reloaded in vivo by reinjecting a solution of BCNU in ethanol into the capsule after implantation. Tests of this preparation against the Brown-Pierce epithelioma in the anterior chamber of rabbit eyes, as compared with control rabbit eyes treated with empty polymers, demonstrated inhibition of tumor growth.

Nitrosoureas have also been investigated as infusional agents. Tator (108) injected lomustine intraneoplastically in a mouse model of ependymoblastoma. He demonstrated that animals treated with intraneoplastic lomustine had improved survival compared with control animals and was superior to the intraperitoneally injected drug.

Garfield et al. (32) infused 1050 mg of BCNU daily for 4 to 40 days in each of 10 patients via catheters implanted within the tumor resection cavities. They reported no evidence of BCNU-related toxicity and had one survivor at 199 weeks. Pathological examination at autopsy showed acute necrosis in the wall of the tumor cavity to a depth of 1.5 cm.

Yamashima et al. (129) investigated nitrosoureas administered into the resection cavities of malignant gliomas from an Ommaya reservoir. They used two partially water-soluble nitrosourea derivatives, nimustine (ACNU) and ranimustine (MCNU). Thirteen patients received 20-mg doses of ACNU repeated 15 times for a total dose of 300 mg. Seven patients received 11 mg of MCNU twice for a total dose of 22 mg. The investigators reported that although ACNU was generally well tolerated, albeit with some side effects, such as headache, nuchal rigidity, vomiting, motor weakness, and cranial nerve palsy, MCNU induced marked brain edema and caused abnormal respiration and arrhythmias. Although the study was designed to examine toxicity from intraneoplastic infusion of these agents, the authors also present their survival data. Survival ranged from 5 to 37 months for patients receiving ACNU and 10 to 26 months for patients receiving MCNU. Sasahira and Ichitubo (98) and Saito et al. (97) have also reported positive results with intratumoral ACNU in small trials (20 and 9 patients, respectively).

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METHOTREXATE (MTX)

Initial clinical trials with MTX as an intratumoral agent were performed in the late 1960s and early 1970s using either an intratumoral catheter (31) or an Ommaya reservoir (42,96,126). In each of these trials, the most significant finding was a nearly uniform lack of toxicity. In the studies by Rubin et al. (96) and Weiss and Raskind (126), each enrolling nine patients, the most significant toxicities noted were bacterial meningitis in one patient (96) and mild leukopenia in two patients (126). No mention was made of extensive necrosis at the infusion site. Garfield and Dayan (31) gave higher doses of MTX, up to 1250 mg per day, in nine patients. The most significant clinical toxicities from the infusions were fever and then a maculopapular rash over the upper trunk and limbs. In six patients, this progressed over 5 days to leukopenia, necessitating withdrawal of therapy. At autopsy, there was a rim of necrotic tissue and increased edema at the site of the intratumoral MTX infusion. Areas of brain distant to the infusion site were unchanged. Thus, MTX seems to be safe for intratumoral infusion.

The first large-scale trials of intratumoral MTX were reported by Diemath in 1987 (23) and Diemath and Hausmaninger (24), in which 269 patients were divided into five groups to receive treatment as follows: 1) surgical resection; 2) resection and radiotherapy; 3) resection, radiotherapy, and systemic chemotherapy; 4) resection and systemic and local chemotherapy; and 5) resection, radiotherapy, and systemic and local chemotherapy. The local MTX was delivered by implantation of a Spongostan matrix soaked with MTX within the tumor cavity, intraoperatively after resection. The methods and agents used for systemic chemotherapy were not provided in the article. The longest median survivals were achieved when resection, radiotherapy, and systemic chemotherapy were combined, regardless of whether local MTX was used. The median survivals for Groups 3 and 5 were 83 and 75 weeks, respectively. Median survivals for Groups 1, 2, and 4 were 10.2, 34.8, and 36.8 weeks, respectively. Although this suggests that local MTX had little effect on overall survival, there were more long-term survivors in the group receiving local MTX than in the other groups. More than 25% of the patients in Group 5 were alive after 200 weeks. In an earlier study, 152 patients who received treatment with the same MTX-soaked Spongostan system, used in conjunction with topical amethopterin, a folic acid antagonist, were also reported to have an extended survival compared with that of patients receiving traditional chemotherapy (24).

In an effort to extend tumor exposure to MTX, Nierenberg et al. (77) and Harbaugh et al. (40) treated five patients with recurrent gliomas by using the Shiley-Infusaid pump to deliver an escalating constant infusion of MTX from 1 to 75 mg per day. The catheter was implanted after stereotactic biopsy in two patients and after surgical debulking in three patients. Patient survival after treatment ranged from 7 to 49 weeks, and there was no consistent evidence of tumor regression, clinically or radiographically. Drug concentrations, intratumorally and throughout the brain, determined from one patient at autopsy and from one after surgical resection demonstrated that MTX was widely distributed throughout the brain. Tumor concentrations ranged from 2,310 to 160,000 ng of drug per gram of brain tissue, whereas brain levels as far as 11 cm from the tip of the catheter were as much as 92 ng of drug per gram of brain tissue. The authors conclude that intratumoral MTX delivery by constant infusion is feasible, with minimal toxicity and wide intracerebral drug distribution.

Although data from clinical trials have indicated that intratumoral MTX is minimally toxic, there are published case reports of toxicity associated with this drug. A 60-year-old woman receiving intraventricular chemotherapy for meningeal carcinoma developed an abulic-hypokinetic syndrome and left hemiparesis (114). Computerized tomography revealed a hypodensity in the right frontal lobe white matter corresponding to focal necrosis resulting from intrusion of the catheter tip into the brain parenchyma. The status of the patient improved with prednisone. Two patients have also been reported to have formation of enlarged cysts at the site of intracavitary therapy with Adriamycin and MTX administered from an Ommaya reservoir (100).

Laboratory investigations of MTX have centered on analyzing the intracerebral biodistribution of MTX after local administration. Tator and Wassenaar (109) examined the intracranial concentration of MTX in mice after intracerebral injection, both with and without tumors present. After injection of ^{3}H-methotrexate, the drug was widely distributed throughout the brain and tumor. After 2 minutes, the drug had been largely taken up intracellularly. Within 1 hour, it had been distributed throughout the mouse brain. When an ependymoblastoma was present, nearly all tumor cells took up the labeled drug. Sendelbeck and Urquhart (99) demonstrated that MTX was distributed throughout the rabbit brain. Drug concentrations 10 mm from a catheter tip were 0.1% of the infused dose. In contrast, two studies, performed by Blasberg (2) and Blasberg et al. (4), demonstrated that when MTX is delivered either by ventriculocisternal perfusion or intraventricularly, MTX is taken up by the ependyma but its penetration into the deep brain is minimal and slow. Thus, intratumoral delivery for this drug seems to have a theoretical advantage over intracerebrospinal fluid methods.

Two experimental reports describe the use of polymeric drug delivery devices to administer MTX. Rama et al. (88) used a polymethylmethacrylate pellet to deliver MTX intracranially in a rat model of glioma (88). Rats bearing intracranial ethylnitrosourea-induced tumors were treated with MTX delivered from the polymethylmethacrylate pellet. The survival of the treated rats improved 69% compared with that of the controls. The drug was quickly released from the matrix, with 96 to 99% of the loaded drug delivered within 2 days after implantation. Zeller et al. (131) reported that a polylactide-MTX

formulation significantly inhibited glioma growth in the rat flank. These formulations have not been evaluated in patients, however.

Dang et al. (22) modified MTX by covalently linking it to dextran via an amide bond. The MTX-dextran amide bond is biologically stable and resistant to degradation. Thus, linked MTX should be eliminated from the brain more slowly than unmodified MTX and should diffuse farther into the extracellular matrix during the period when the molecule is biologically active, improving its activity versus that with brain tumors. We found that the MTX-dextran amide conjugate was equipotent with unmodified MTX versus brain tumor cell lines in vitro. The conjugate could penetrate into a three-dimensional collagen matrix that was similar to the extracellular matrix significantly better than unmodified MTX could. Furthermore, when the modified MTX was intratumorally delivered to rats with intracranial glial tumors, it was able to improve the survival of rats with tumors compared with that of controls. Chemical modification of drugs delivered from polymer implants is, therefore, a promising method for maximizing the tumoricidal activity of locally delivered chemotherapeutic agents by maximizing their diffusion into tumor tissue.

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BLEOMYCIN

Experimental evidence supporting the intratumoral use of bleomycin is based on several studies. Hayakawa et al. (41) reported on bleomycin uptake by various forms of brain tumors in 67 patients given systemic bleomycin before surgical resection. The tissue removed during surgery was assayed for bleomycin. Although almost all of the tumor (49 of 53 samples) and cyst (17 of 18 samples) samples collected from these patients contained detectable bleomycin, the level of the drug varied greatly from 0 to 1.25 μg/g in solid tumors and 0 to 3.5 μg/ml in cyst fluid. Peritumoral brain removed at operation, however, showed no detectable bleomycin (14 samples). Intratumoral delivery is, therefore, more likely than systemic delivery to deliver the drug to the tumor bed.

Experiments in rat models by Vats et al. (115) and Kimler et al. (53) have examined the efficacy of intracerebral compared with intravenous bleomycin against intracranial glioma. They discovered that intracerebral bleomycin improved rat survival, whereas intravenous doses five times as high had no effect. The effect was magnified when combined with external beam radiotherapy in the rat.

Bleomycin has been administered from an Ommaya reservoir in malignant brain tumors in three pilot studies. Bosch et al. (6) initially infused 400 μg of bleomycin labeled with ^{111}Indium, intratumorally, in three patients. Each patient then received three doses of 5 mg of bleomycin, intratumorally. Of these three patients, two died after 3 and 5 months, respectively, from tumor growth, whereas one was still alive after 2 years when the report was published. No pharmacokinetic data were reported. The major toxicity from the trial was a sudden rise in intracranial pressure after infusion in one patient, necessitating emergent surgery. Thereafter, the patient was well until the tumor recurred.

Nakazawa et al. (75) treated 12 patients with malignant brain tumors, of whom 9 had gliomas, 1 had oligodendroglioma, 1 had sarcoma, and 1 had medulloblastoma. He administered 0.1 to 0.2 mg/kg of bleomycin every other day for a total dose of 30 to 80 mg of the drug. The overall survival rate was 50% at 1 year and 25% at 3 years, with the patients without gliomas accounting for the three survivors. As part of the study, the authors injected [^{57}Co]bleomycin and measured its clearance from the tumor site. Approximately 70% of the intraneoplastic bleomycin was cleared by 2 to 4 days after administration, whereas 70% of the administered drug was cleared within 2 to 4 hours after intravenous administration. Although this indicated that bleomycin was retained in the tumor longer with intraneoplastic injection, bleomycin could only penetrate 2 to 3 cm into the brain parenchyma from the infusion site. The authors concluded that intratumoral bleomycin had definite activity versus brain tumors but that it should be combined with other intra-arterial or intravenous agents.

Morantz et al. (73) treated eight patients with gliomas with bleomycin from an Ommaya reservoir. Each patient received 5000 to 6000 rads of whole brain radiation therapy before surgical resection for maximal tumor removal.

An Ommaya device was then placed within the tumor reservoir, and 2.5 to 10 units of the drug were given once per week as a continuing therapy. Patients receiving the drug for up to 16 months had no significant side effects. One patient, receiving the highest dose of bleomycin, experienced headache and lethargy 3 days after his third injection. Computerized tomography revealed extensive edema around the tumor bed, and the patient was treated with corticosteroids, which resulted in prompt resolution of the edema. Three of the eight patients were alive more than 1 year after the start of therapy.

Bleomycin administered from an Ommaya reservoir has also been reported to be used against craniopharyngiomas in children (102). Takahashi et al. (102) treated seven patients aged 2 to 13 years who had cystic tumors with right frontotemporal craniotomies for aspiration of the cyst fluid; only enough tissue was taken from the cyst wall to histologically confirm the diagnosis. The Ommaya catheter was inserted into the cyst, and bleomycin labeled with ^{57}Co was injected into the tumor to measure drug uptake into the tumor. Bleomycin clearance from the cyst was relatively rapid with a $t_{1/2}$ of 3 hours and 10% of the initial activity present 24 hours after injection. Each patient then received 1 to 5 mg of bleomycin percutaneously injected into the reservoir every other day. At each injection, 2 to 3 ml of cyst fluid was withdrawn and examined biochemically. Four patients with cystic tumors were alive at 5 years follow-up with normal quality of life, but three patients with mixed or solid tumors died. The authors conclude that local therapy with bleomycin may have a role in the treatment of cystic craniopharyngiomas.

In an attempt to improve on simple intratumoral bleomycin infusions, Firth et al. (29) prepared a liposomal preparation of bleomycin and compared its pharmacokinetics with that of free bleomycin when injected intracerebrally in the rat brain. They reported that 35.1 to 76.2% of an injected bleomycin dose was retained intracerebrally after 4 hours when it was encapsulated, compared with only 2.6 to 20.3% of the free bleomycin. Brain levels remained elevated for as long as 24 hours, with 11.8% of the liposomal bleomycin retained intracerebrally, compared with 0.9 to 1.3% of the free bleomycin. The authors report that liposomal bleomycin induced a mild inflammatory reaction that was not present with free bleomycin or buffer. On the basis of their results in rat models, McKeran et al. (68) tested the

liposomal bleomycin preparation in three patients with gliomas; they reported no discernible toxicity from the preparation but presented no survival data.

Katakura et al. (51,52) have reported on a controlled-release preparation for bleomycin composed of a compressed form of lactose encapsulated with ethylcellulose or Eurdragit. When the tablets were implanted in the cerebrums of dogs, the release half-life was 11 days and bleomycin was detectable in the cerebrospinal fluid up to 20 days after implant. They tested this preparation intracranially in a model in Wistar rats with intraperitoneal glioma tumors and demonstrated that the tablet preparation was superior to the simple intraperitoneal bleomycin injection at preventing tumor growth. The tablet has been used in six patients with craniopharyngiomas.

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5-FU

Ringkjøb (91) reported on the intratumoral administration of cytostatic agents to patients with malignant brain tumors in 1968. He treated 40 patients with supratentorial recurrent malignant brain tumors, of whom 32 had Grades 3 to 4 astrocytomas and the remaining had lower-grade astrocytoma, sarcoma, oligodendroglioma, or metastasis. After subtotal resection of the tumor, he implanted gelatin sponges or Surgicel loaded with 5-FU (19 patients), 5-FU with the methylenehydrazine derivative Natulan (16 patients), Natulan alone (1 patient), or thiotepa (4 patients). Although Ringkjøb observed no cytotoxicity from the treatment, he was not able to demonstrate any therapeutic effect either. Of 16 patients with Grades 3 to 4 astrocytomas receiving 5-FU alone, only 4 lived longer than 6 months. Two of the 12 patients with Grades 3 to 4 astrocytomas receiving 5-FU with Natulan survived longer than 6 months. The longest survivor receiving thiotepa lived 16 months, and the patient receiving Natulan alone died after 4 months. Ringkjøb concluded that although intratumoral chemotherapy was theoretically attractive, none of these agents seemed to be good candidates for further investigation. Furthermore, Surgicel and gelatin foam do not release drugs in a sustained fashion; survival may have been improved if a controlled-release matrix were available.

Oda et al. (82) incorporated 5-FU and urokinase into a Silastic tube and showed that it was capable of releasing both drugs constantly and continuously for 5 weeks. Trials of this preparation in rats against ethylnitrosourea-induced gliomas demonstrated that it was capable of completely inhibiting tumor growth in the rat flank. In an initial clinical trial with 14 patients with malignant gliomas and metastatic carcinoma, all but 1 patient lived more than 8 months after implantation. Further clinical trials (81,83) with the preparation have included 250 mg of 5-FU, 6000 IU of urokinase, 1.5 mg of mitomycin C, and 250 mg of bromodeoxyuridine. As of 1985, 136 patients had been treated with this preparation. The median survival for patients with malignant gliomas was 18 months (1-yr survival rate, 66%; 3-yr survival rate, 16%). Pharmacokinetic measurements indicated that tumoricidal levels of 5-FU were present as long as 2 years after implantation but that cerebral drug penetration was insufficient to inhibit tumor growth 5 cm from the implanted pellet.

Kubo et al. (56) have also used a polymeric delivery system for intratumoral 5-FU chemotherapy. They incorporated 5-FU, ACNU, Adriamycin, or mitomycin C into a matrix consisting of "glassified monomers" with 10% polymetacrylic methyl acid. They implanted these agents into 55 patients and achieved a 47% 1-year survival rate in patients with malignant gliomas.

Fewer studies have examined 5-FU for intratumoral infusion as opposed to polymer implants. Penn et al. (86) examined chronic 5-FU infusion from an osmotic mini-pump to treat 9L glioma in the rat brain and demonstrated that this procedure was able to prolong survival 87% compared with control animals.

Continuous infusion of a related drug, fluorodeoxyuridine, from a Medtronic SynchroMed pump has been used to treat a single patient with an intracranial renal cell carcinoma metastasis (21). The patient had a complete response within 3 months of the treatment and maintained the response for 22 months. Choti et al. (18) have demonstrated that fluorodeoxyuridine can be successfully delivered from FAD-SA polymers both in vitro and in vivo.

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ADRIAMYCIN

Adriamycin is an anthracycline antitumor antibiotic that possesses a number of tumoricidal activities, including the ability to intercalate with deoxyribonucleic acid, resulting in strand scission and double-stranded cross breaks (16). Itoh (47) used an Ommaya reservoir after surgical resection to deliver Adriamycin to the tumor bed in 22 patients with malignant gliomas. Aliquots of 0.5 mg of Adriamycin were periodically injected into the Ommaya reservoir for a total Adriamycin dose of 5.0 mg. The local chemotherapy was combined with cobalt-60 irradiation and immunotherapy. They achieved a 1-year survival rate of 41% and a 2-year survival rate of 13%. Kinetic measurements indicated that the concentration of Adriamycin in the tumor was 8 to 38 times higher than that achieved by intravenous injection of Adriamycin. The drug penetrated ~3 cm into the brain parenchyma.

Lin et al. (62) developed polymer-based delivery of Adriamycin by using EVAc needles. The matrix was capable of delivering Adriamycin with zero order release in vitro and significantly inhibited growth of brain tumor xenografts in nude mice. This method has not been reported in patients.

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PLATINUM DRUGS

Bouvier et al. (7) described a patient with recurrent glioma treated with cisplatin infused through multiple catheters implanted within the tumor bed. They had previously demonstrated that cisplatin chronically infused intratumorally could prolong survival by 27% in a rat glioma model (86). As described in the case report, they implanted 68 individual catheters evenly throughout the tumor and infused cisplatin at a constant rate of 12 μg per catheter per day for 10 days. Each catheter was connected to a separate individual pump. A CT scan performed 2 months after infusion showed slightly less mass effect, but by 5 months, the tumor showed signs of recurrence and the patient experienced a rapid deterioration to death.

Although the response in this patient was disappointing, the technique presented has several advantages over simpler intratumoral infusion schemes that use a single catheter. Kroin and Penn (55) had previously demonstrated that the brain penetration of cisplatin from a single catheter tip is only 1 cm. By implanting multiple sources, the amount of drug penetration into the tumor is increased. Also, by using constant rather than intermittent infusion, the diffusion gradient is maintained, giving better drug distribution away from the catheter tip. Theoretically, these characteristics should improve the activity of the infused drug.

We have recently presented an alternative approach for delivering platinum drugs (26). We incorporated carboplatin, a second-generation platinum analog that is less neurotoxic than its parent compound, cisplatin (85), into a biodegradable polyanhydride matrix consisting of a FAD-SA (ratio, 50:50). In vitro, 70 to 80% of the loaded drug was released from the matrix over 4 to 5 weeks. When implanted intracranially, the carboplatin FAD-SA matrix improved median survival 3.3-fold in rats bearing intracranial F98 gliomas. Final preclinical evaluations of this preparation are underway in preparation for clinical trials.

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OTHER CYTOTOXIC AGENTS

Several cytotoxic chemotherapeutic agents have been evaluated for intratumoral chemotherapy for gliomas in the laboratory, but have yet to be used clinically. We have used taxol, a novel microtubule-binding agent, delivered from the PCPP-SA polymer against experimental intracranial gliomas in the rat. Taxol has shown good activity against several human neoplasms in clinical trials (95) and has good activity versus brain neoplasms in vitro (15). Unfortunately, taxol has been shown not to cross the intact blood-brain barrier (54,94). Incorporating taxol into a biodegradable polymer enables the drug to bypass the blood-brain barrier. We found that taxol released from an intracranial polymer implant was capable of extending survival 1.5- to 3.1-fold ($P < 0.05$ and $P < 0.002$, respectively) versus control animals when delivered from the intratumoral implant. Furthermore, the implant maintained tumoricidal taxol concentrations within

the brain for more than 1 month after implantation (120). Biodegradable polymers can, therefore, expand the number and types of chemotherapeutic agents that can be used for intracranial neoplasms.

Cytoxan is the most widely used antineoplastic agent in clinical use (19); however, to be used against gliomas, cytoxan must be given at high doses, resulting in severe systemic toxicity. High doses are required because the active metabolite of cytoxan, hydroxycyclophosphamide, crosses the blood-brain barrier poorly. Unfortunately, cytoxan is a poor candidate for local therapy as well because it requires enzymatic activation by the p450 cytochrome oxidase system of the liver. The parent compound has no antitumor activity. To exploit the antitumor activity of cytoxan and circumvent the limitations of the blood-brain barrier, Judy et al. (50) and Domb et al. (26) have reported the use of 4-hydroperoxycyclophosphamide (4-HC) against intracranial F98 gliomas in rat models. 4-HC spontaneously degrades in vivo to hydroxycyclophosphamide, the active antitumor metabolite of cytoxan (20). The drug was incorporated into a polymer matrix consisting of a FAD-SA. In this instance, the matrix both served as a controlled-release matrix and protected the 4-HC from spontaneous degradation before release. Measurements of 4-HC release from the FAD-SA polymer implant in vivo in the rat brain demonstrated an early burst of release after implant and then peak intracerebral concentrations of the drug 5 to 20 days after implantation (14). When rats with intracranial F98 glial tumors were treated with the polymer composed of FAD-SA and 4-HC, the median survival of treated rats, compared with control rats receiving empty polymers, was extended (77 versus 14 d).

Recently, we have also reported that camptothecin, a topoisomerase I inhibitor, extended survival in a rat model of malignant glioma (125). Rats that received intracranial EVAc copolymers containing camptothecin survived significantly longer than rats that received control polymers. Systemically administered camptothecin had no effect on survival in these models.

Another experimental therapy was reported by Oliver et al. (84), who incorporated vincristine into liposomes and measured the toxicity and retention of the preparation within the cerebral parenchyma after intracranial

injection in rats. They concluded that liposomes can serve as a depot for vincristine and block its elimination from the brain.

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IMMUNOTHERAPY

Immunotoxin therapy uses a covalent construct containing a toxic moiety and a ligand that is specific for a receptor selectively expressed on cancer cells. Theoretically, the ligand portion of the immunotoxin binds selectively to a cancer cell receptor and the toxin moiety kills the tumor cell. In a recent review of the literature, Hall and Fodstad (39) enumerated several experimental immunotoxin preparations that are under investigation for glioma therapy. The most commonly examined preparations contain ligands for either the epidermal growth factor receptor or the transferrin receptor, both of which are overexpressed in glial tumors, complexed to a wide variety of toxins including ricin, diphtheria toxin, and *Pseudomonas* exotoxin. Unfortunately, these antibody-toxin conjugates may penetrate the blood-brain barrier poorly because of their large molecular weights. Hence, intratumoral administration may be the best method for delivering these agents. Phillips et al. (87) demonstrated that intracranial intratumoral injection was more effective than intraperitoneal injection of a transforming growth factor α-*Pseudomonas* exotoxin fusion protein at prolonging the survival of nude mice with intracranial gliomas. Studies are underway to evaluate the polymeric delivery of immunotoxins directly to glial tumors.

Cytokines exhibit a wide variety of powerful biological effects that have potential as antitumor therapies. Martinez et al. (66) reported on 10 patients whom they infused intratumorally (8 patients) or intraventricularly (2 patients) with human lymphoblastoid interferon (IFN)-α. Although the treatment was well tolerated, the authors reported no difference in survival compared with historical controls and the CT scans showed rapid progression of tumor growth in all patients. Watts and Merchant (121) investigated intratumoral interleukin-2 (IL-2) in conjunction with intravenous chemotherapy and concluded that intratumoral IL-2 potentiated the effects of several chemotherapeutic agents. Merchant et al. (71) also infused IL-2 intratumorally via an Ommaya reservoir in nine patients, four of whom were

also treated with subcutaneous injections of IFN-α. Three of the five patients receiving IL-2 alone had tumor progression during the treatment interval, whereas none of the patients receiving IL-2 therapy with concurrent IFN-α experienced tumor progression. Side effects from the therapy included fatigue, muscle weakness, and nausea. On the basis of the results of the study, the authors concluded that IL-2 merited further investigation as an intratumoral therapy.

Färkkilä et al. (28) investigated intratumoral recombinant IFN-γ as a therapy for gliomas. Twenty-seven patients were randomized to receive either surgery, radiotherapy, and intratumoral IFN-γ or surgery and radiotherapy alone. Although the IFN-γ infusions were well tolerated, with transient fever being the only significant side effect, the authors reported no improvement in patient survival. The median survival for patients in the valid study group was 54 weeks for the control group and 55 weeks for the IFN-γ groups. Although IFN-γ seemed to be inactive in this study, the authors allow that the doses they used were low in comparison with the use of IFN-γ in clinical trials with other malignancies. They also mention that IFN-γ may have an adjuvant role in addition to other chemotherapeutic strategies.

Adoptive immunotherapy involves intratumorally infusing lymphocyte-activated killer (LAK) cells. These cells have the ability to kill tumor cells selectively, while leaving normal cells untouched. Their activity can be augmented with the simultaneous administration of cytokines or activating antibodies. Naganuma et al. (74) reported a complete regression of a glioblastoma multiforme in one patient treated with intratumoral LAK cells, IFN-β, and ACNU. Merchant et al. (72) treated 20 patients with intratumoral LAK cells and IL-2. At the time of publication, seven of the tumors of these patients had recurred after a median disease-free survival of 25 ± 6 weeks, whereas eight patients continued to be disease free after 6 months or more. Nitta et al. (80) infused LAK cells that had previously been activated by exposure to an anti-CD3 monoclonal antibody. Of 10 patients, 4 patients had partial and 4 had full regressions with the therapy and all 8 of these patients were alive 10 to 18 months after therapy. Jeffes et al. (48) used IL-2 and phytohemagglutinin to activate and improve the cytotoxicity of mitogen-activated killer cells in 16 patients. Thus, concurrent intratumoral chemotherapy may augment the effectiveness of adoptive immunotherapy.

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EXPERIMENTAL THERAPIES

The explosion in the understanding of tumor biology over the last 2 decades has expanded the number of potential tumor targets for chemotherapy and correspondingly widened the varieties of available therapies. These have included antiangiogenesis agents, immunotoxin therapy, immunotherapy, gene therapy, and other biological response modifiers. Because many of these preparations act locally, they have been initially evaluated as intratumoral therapies.

Angiogenesis inhibition restricts tumor growth by inhibiting its blood supply (37). We have incorporated angiogenesis inhibitors into sustained-release polymers. Both heparin-cortisone and minocycline incorporated into EVAc copolymers blocked neovascularization in the rabbit cornea stimulated by a VX2 carcinoma implant (103,105). When minocycline was incorporated into controlled-release polymers and intracranially implanted in rats simultaneously implanted with 9L gliosarcoma tumors, it improved survival and, in addition, showed a synergistic effect with systemically given BCNU (123,124). These results were consistent with those of Teicher et al. (110), who showed that antiangiogenetic agents, such as minocycline, were capable of potentiating the effects of several chemotherapeutic agents in a mouse model of metastatic carcinoma. Locally delivered angiogenesis agents may be useful adjuvants to improve the tumor destruction induced by other modalities.

Malignant gliomas induce significant cerebral edema secondary to breakdown of the blood-brain barrier. High-dose corticosteroid therapy (67) is usually able to control cerebral edema associated with tumors; however, such therapy is associated with several major side effects, including diabetes, weight gain, hemorrhagic ulcers, skin atrophy, myopathies, osteoporosis, and pathological fractures (69). We have shown that a controlled-release polymer intracranially implanted in the rat can release dexamethasone for up to 21 days (90,101,107,119). The intracerebral steroid concentrations from the polymer are several orders higher than could be achieved with systemic intraperitoneal injections and produce only a fraction

of the systemic steroid levels. Theoretically, the implant could reduce the systemic toxicities of dexamethasone therapy. Furthermore, this implant was as effective as systemic dexamethasone at reversing cerebral edema in a rat model of tumor-induced edema. By altering the release properties of the polymer matrix, even longer release periods should be obtainable. Controlled-release steroid therapy could be a method for controlling one of the most significant consequences of gliomas, while limiting the toxicities of the therapy.

Ronquist et al. (92) used L-2,4-diaminobutyric acid delivered from microdialysis probes implanted intratumorally in three patients. L-2,4-diaminobutyric acid is a novel chemotherapeutic agent that is selectively taken up by glioma cells because of their enhanced ability for substance transport. The drug induces osmotic lysis of cells. After infusion, the investigators noted significant tumor necrosis on serial CT scans, which they took as evidence of tumor regression. They report no side effects from the therapy. The three patients lived 7, 16, and 17 months after therapy.

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DISCUSSION

Significant technical advances have been made in the field of intratumoral chemotherapy within the last decade. In several of the studies reviewed, investigators clinically and experimentally confirmed that sustained-release polymers and pumps are capable of delivering higher concentrations of a wide variety of drugs to the CNS than can be obtained by systemic delivery (36,75,77,82,83,120). These drug concentrations could be maintained for extended durations. This is significant, because it removes the blood-brain barrier as an obstacle to antiglioma chemotherapy and expands the types of cytotoxic agents available for use against gliomas. Agents such as carboplatin, cytoxan, and taxol that are highly active in vitro but excluded by the blood-brain barrier, could now be used as intratumoral agents (15,50,85,120). Newer experimental agents, such as immunotoxins, tumor vaccines, cytokines, and angiogenesis inhibitors, that possess complex polypeptide structures and mechanisms that are innately unsuitable for systemic delivery will realize their role in glioma therapy largely through

intratumoral approaches. New discoveries and improvements in programmable pumps and controlled-release polymers will optimize the delivery profiles for these agents.

Equally important, a wide variety of chemotherapeutic agents seem to be amenable to local tumor-based strategies. In each of the reports reviewed, there was a uniform lack of significant toxicities resulting from intratumoral approaches. The severity of local toxicity and tissue necrosis from most drugs, such as BCNU and MTX, seems to be comparable to that from interstitial radiotherapy (10,31,32). Furthermore, intratumoral implants do not seem to be associated with significant risks of infection (11). Also, by targeting chemotherapy directly to the tumor, systemic drug levels may be reduced. The dangerous dose-limiting side effects of chemotherapeutic agents, such as anemia, thrombocytopenia, leukopenia, stomatitis, nausea, and vomiting, may be substantially reduced by intratumoral protocols. Thus, the quality of life of the patient may be maintained during therapy. Lengthy hospital stays to treat these complications may also be avoided and overall health care costs reduced.

Additionally, the cost of adapting pre-existing drugs for use with intratumorally based therapies is substantially less than the cost of developing new drugs. It has been estimated that bringing a new drug to clinical use costs more than 150 million dollars. Alternatively, it costs significantly less to adapt a pre-existing drug to use with a new drug delivery system. Thus, intratumoral chemotherapy is an attractive research arena because it maximizes the return on health care expenditures.

Finally, the survival benefits associated with intratumoral chemotherapy seem to be promising. A recent multi-institutional, prospective, randomized, placebo-controlled study documented a significant improvement in survival for patients with recurrent malignant gliomas treated with intratumoral BCNU released from a biodegradable polymer (11). Two other large-scale studies have demonstrated either increased median survival (81) or increased numbers of long-term survivors (23). Future studies will determine the best method for incorporating intratumoral chemotherapy with other therapeutic modalities. Initial clinical trials are usually performed with patients who have failed to benefit from existing therapies. Now that

controlled-release BCNU polymers have shown a survival benefit for patients with recurrent malignant gliomas, they must be tested as initial therapies and in conjunction with radiotherapy and other modalities. Initial data in Phase I trials indicate that combination therapy is safe, and we will pursue studies of these protocols in Phase II and III trials. We have previously outlined an algorithm for treating patients with malignant gliomas incorporating surgery, local therapy at surgery, radiotherapy, and additional therapies (Figure 2) (122). As more studies are performed, the appropriate role and timing for intratumoral chemotherapy will become increasingly clear.

A theoretically attractive scheme for the clinical use of intratumoral chemotherapy would be in conjunction with in vitro chemosensitivity tests. Protocols have been developed for culturing tumor specimens removed during surgery and assaying them for sensitivity and resistance to chemotherapeutic agents (5,78,79). Potentially, a biopsy specimen could be taken stereotactically from a patient and cultured for drug sensitivity. At the time of definitive surgery, a polymer disc or infusion pump could be placed within the resection cavity to deliver the drug or drug combination appropriate for the patient's tumor. The process could then be combined with external beam radiotherapy and appropriate systemic therapies.

Although it is true that an in vitro sensitivity is not a guarantee of an in vivo effect, studies have indicated there is a correlation between the two (30), particularly in predicting tumor resistance to chemotherapy. For in vitro sensitivity and resistance to chemotherapy using a colony-forming assay, Tonn et al. (112) studied the tumors from 33 consecutive patients operatively treated for malignant gliomas at their institution. They found that the assay had a predictive value of 70.6% for a positive tumor response and 86.7% for a negative tumor response to chemotherapy.

At the time of recurrence, a new biopsy would be obtained to study the tumor again and to analyze its new sensitivity and characteristics. On the basis of these results, the treatment cycle would be reinitiated. As more polymer-chemotherapy combinations become available, these types of approaches would enable clinicians to design specific therapies to optimize clinical

responses in individual patients and at different time points in the disease process.

Despite these advances with intratumoral chemotherapy, several challenges remain. The efficacy of many currently available chemotherapeutic agents against gliomas may be limited. Although intratumoral chemotherapy can improve the pharmacokinetic properties of an agent, it can not overcome inherent or acquired tumor resistance to chemotherapeutic agents. We hope that the development of newer agents as well as delivery methods will progress to optimize treatment for gliomas. As more selective and sophisticated chemotherapeutic agents, such as immunotoxins, cytokines, and angiogenesis inhibitors, are developed, local delivery schemes will become available to optimize their activity.

Additionally, intratumoral chemotherapy is limited by the physicochemical properties of the compound being delivered. Although intratumoral chemotherapy delivers the drug to the tumor target, its ultimate efficacy also depends upon the postrelease properties of the drug, namely its ability to diffuse into brain parenchyma, its uptake into tumor cells, and the speed with which it is cleared from the CNS after release. Chemically modifying existing drugs so that their diffusion penetration is maximized and brain clearance is minimized can improve their activity in conjunction with controlled release. Studies such as that by Dang et al. (22) seek to address this issue by chemically modifying existing drugs to improve their brain penetration. We hope that other chemotherapeutic agents will be amenable to this approach as well.

Although virtually any drug can be delivered intratumorally as long as it does not possess overwhelming local toxicity, more research must be performed to determine the optimum delivery profiles for individual drugs. Although prolonged drug delivery is generally desirable, it is possible that this may induce resistance within the tumor to certain drugs. Intermittent-release polymers or pumps may be desirable for certain drugs to guard against this phenomenon. In addition, although altering the delivery characteristics of polymers and pumps yields a vast array of delivery schema, there remains no other method of predicting response to each profile than empiric trial and error. We hope that sophisticated mathematical models of drug delivery, drug

brain penetration, and tumor uptake will enable the most efficient delivery method to be determined individually for each drug.

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CONCLUSION

Intratumoral chemotherapy is an attractive method for treating patients with brain tumors. It can bypass the blood-brain barrier, minimize systemic drug levels and toxicities, and maintain elevated intracranial drug concentrations for extended periods. The side effects of the therapy seem to be mild across the spectrum of chemotherapeutic agents used. Large-scale clinical trials have demonstrated improved survival in patients receiving intratumoral chemotherapy with biodegradable implants compared with patients receiving control implants (11,23). As more chemotherapeutic and biologically active agents become amenable to local delivery, alone or in combination, and as drug delivery polymers and pumps become more sophisticated, there is reasonable hope that local therapy will play an increasing role in the management of patients with brain tumors.

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