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Biodegradable polymer implants to treat brain tumors

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Abstract

We have developed a systematic approach for the discovery and evaluation of local treatment strategies for brain tumors using polymers. We demonstrated the feasibility of polymer-mediated drug delivery by using the standard chemotherapeutic agent 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU) and showed that local treatment of gliomas by this method is effective in animal models of intracranial tumors. This led to clinical trials for glioma patients, and subsequent approval of Gliadel™ [(3.8% BCNU): p(CPP:SA)] by the FDA and other worldwide regulatory agencies. Twenty-two additional clinical trials are currently underway evaluating other issues related to the BCNU polymer, such as dosage, combination with systemic treatments, and combination with various forms of radiation and resistance modifiers. These trials are a result of laboratory investigations using brain tumor models; based on these models, other research groups have initiated clinical trials with novel combinations of different drugs and new polymers for both intracranial tumors (5-fluorouracil delivered via poly(D-L lactide-co-glycolide) polymer) and for tumors outside the brain (paclitaxel in PPE microspheres for ovarian cancer). Since only 1/3 of patients with glioblastoma multiforme (GBM) are sensitive to BCNU, the need to search for additional drugs continues. Although we are attacking major resistance mechanisms, there still will be tumors that do not respond to BCNU therapy but are sensitive to agents with different mechanisms of action, such as taxanes, camptothecin, platinum drugs, and antiangiogenic agents. Thus, it is necessary to explore multiple single agents and ultimately to combine the most effective agents for the clinical treatment of GBM. Furthermore, multimodal approaches combining radiotherapy with microsphere delivery of cytokines and antiangiogenic agents have demonstrated encouraging results.

Keywords: Brain tumor; Glioma; Local drug delivery; Implantable polymer; BCNU

We have developed a systematic approach for the discovery and evaluation of local treatment strategies for brain tumors using biodegradable polymers. Despite enormous advances in imaging and surgical techniques over the past several decades, we have not seen a concurrent improvement in survival of patients afflicted with primary malignant brain tumors [1–3]. The dismal prognosis of these patients was especially disturbing in view of the development of numerous therapeutic approaches that appeared promising in the laboratory, yet did not prove beneficial to patients when tested in the clinic.

We hypothesized that better delivery of effective therapeutic agents to target sites would improve outcomes. To solve this problem, we developed a method for targeted and controlled delivery of drugs using polymers. Our efforts in this direction were greatly bolstered by the establishment of a National

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Cooperative Drug Discovery Group (NCDDG) by the National Institutes of Health devoted to the study of controlled release polymers for brain tumors. The NCDDG is a multi-disciplinary group currently in its 12th year of funding. It consists of multiple specialties, including our group from Johns Hopkins, evaluating efficacy and neurotoxicity; Robert Langer, Professor of Chemical Engineering at MIT, developing new polymers; Mark Saltzman, Professor of Chemical Engineering at Cornell University, evaluating pharmacokinetics in modeling of drug distribution from point sources in the brain; Mike Colvin, Professor of Oncology at Duke University, developing new therapeutic agents; Drew Pardoll, Professor of Oncology at Hopkins, developing immunologic approaches to treating brain tumors; Craig Smith at Guilford Pharmaceutical, developing formulations and in vitro testing of new polymer formulations; and Mary Wolpert of the National Cancer Institute, acting as the NCI coordinator and facilitator. In addition, Dr. Wolpert has been able to provide us with new therapeutic agents through the National Cancer Institute.

This group has worked successfully over the past decade to develop agents and clinically test treatments that can be best utilized by direct delivery into the brain. As the clinical development has evolved, we have returned to the laboratory to address new issues in order to improve this approach. In order to test the concept that controlled drug delivery would be a more effective and safer means of delivering chemotherapeutic agents to the brain, clinical trails were initiated in 1987. The frequently utilized drug carmustine (BCNU), was utilized in a controlled delivery polymer, poly[bis(p-carboxyphenoxy) propane with sebacic acid p(CPP:SA). The polymer protected the BCNU from degradation. If BCNU is given systemically, its half-life is about 12 min. By contrast, when delivered by polymer, the concentration of BCNU was not only log orders higher in the brain than achievable by systemic administration, but the drug was also delivered over a period of 2–3 weeks and with minimal systemic toxicity. Furthermore, as the surgical cavity was covered with BCNU polymer, the target cells were exposed directly to the therapeutic agent.

The first study was a Phase I-II dose escalation study which demonstrated that, despite the extremely high local concentrations of chemotherapeutic agent, this approach was safe and quite promising in its effectiveness [4]. Therefore, a prospective, randomized, placebo-controlled trial of safety and efficacy of intraoperative controlled delivery was carried out in 27 institutions with 222 patients [5]. One-hundred and ten patients received Gliadel™ wafer and 112 patients received the placebo polymer. Six months after operation, 56% of the glioblastoma patients were alive as compared to 36% of the placebo group patients ($P=0.002$). The Gliadel™ wafer did not lower the performance status or neurologic condition compared to placebo wafer.

Having demonstrated the safety and efficacy of the chemotherapy polymer implants for recurrent disease, we initiated a study utilizing the Gliadel™ wafer as the initial therapy for malignant brain tumors. A Phase I study was carried out with 22 patients demonstrating the safety of the polymer in combination with external beam radiation therapy [6]. This was followed in Europe by a trial conducted by Simo Valtonen, in which 32 patients were enrolled in a randomized placebo-controlled study to evaluate carmustine loaded polymers as the initial therapy followed by radiation therapy [7]. Median survival of the Gliadel™ polymer group was 58 weeks as compared to 40 weeks for the placebo–polymer group ($P=0.012$). Two years after implantation, 31% of the patients that had received the Gliadel™ wafer were alive, compared to 6% of the patients receiving the placebo polymer. Three years after implantation, 25% of the treatment group patients were alive, as compared to 6% of the placebo group patients. A more current study involving 240 patients from multiple countries was recently reported by Professor M. Westphal from Germany [8]. He reported median survival of 60 weeks in the Gliadel™ treatment group as compared to 50 weeks in the placebo group ($P=0.03$).

In summary, these studies demonstrate that BCNU biodegradable polymers can be used safely and effectively at initial presentation and at recurrence. At present, Gliadel™ has received regulatory approval in 22 countries.

A number of clinical lessons have been learned from the use of Gliadel™ wafers for treatment of malignant gliomas. Prior to the insertion of polymer wafers, it is crucial to maximize surgical debulking. Some openings in the ventricles do not preclude the use of Gliadel™ wafers. At the same time, achieving

a water-tight closure of the dura is essential to eliminate cerebrospinal fluid (CSF) leaks and to decrease risk of infection. It is also important to utilize preoperative anti-convulsants and high dose steroids, as necessary, for neurologic compromise. Moreover, steroid therapy must be continued for at least 2 weeks post-operatively.

After validating the 'proof of principle' that controlled release with polymers directly to the brain is safe and effective in improving clinical outcomes, a number of clinical questions concerning Gliadel™ wafers are being addressed in the more than 22 clinical trials currently underway. For example, the issue of whether 3.8% carmustine is the ideal dose for Gliadel™ wafers has been explored in an NIH-funded clinical trial led by Dr. Alessandro Olivi. Laboratory work has demonstrated a direct dose–response relationship for carmustine wafers whereby treatment groups receiving higher loading doses of BCNU exhibit a significant improvement in both median survival and percentage of long-term survivors [9]. Therefore, a clinical dose escalation study was recently carried out demonstrating that up to 20% loaded BCNU (five times the currently available clinical dose) is safe in recurrent malignant glioma [10]. Additional Phase III studies are planned to evaluate the added efficacy of BCNU wafers at the established maximum tolerated dose.

Since the majority of newly diagnosed intracranial tumors are metastatic neoplasms, Ewend et al. have explored local delivery of chemotherapy and concurrent external beam radiotherapy in metastatic brain tumor models [11,12]. Their studies showed that in certain models of common intracranial metastatic tumors, high dose local chemotherapy alone and in combination with concurrent radiation therapy significantly prolonged survival. On this basis, Ewend and colleagues have carried out a three-institution Phase I clinical trial documenting safety and a suggestion of increased efficacy for metastatic carcinoma in patients [13]. An NIH-funded clinical trial utilizing Gliadel™ for metastatic disease is currently underway.

Advances in our understanding of brain tumor biology and improvements in localized drug delivery have led to more effective and less toxic chemotherapeutic agents for use against malignant brain tumors. However, a major limitation of chemotherapy with BCNU (or similar alkylating agents) involves a resistance mechanism mediated by a DNA-repair enzyme, O^6-alkylguanine-DNA alkyltransferase (AGAT). This DNA-repair protein is inherent to a majority of human brain tumors, and protects tumor cells from the cytotoxic effects of alkylating agents [14,15]. Laboratory studies have suggested that O^6-benzylguanine may reduce the resistance to nitrosoureas [16–18]. Currently, NIH funded clinical studies are underway to explore the safety and efficacy of preoperative treatment with O^6-benzylguanine in combination with Gliadel™. Additionally, studies in the laboratory have suggested that combination chemotherapy with Gliadel™ will prove even more effective, and numerous clinical studies are underway to explore the possible benefit of combining systemic chemotherapy with the local delivery of BCNU in the operating room [19,20].

Other approaches, such as the delivery of cytokines for immunotherapy, delivery of antiangiogenic agents, and newer chemotherapeutic agents are all being explored in the laboratory with the hope of developing these therapies for brain tumor patients [21–25]. In addition to having demonstrated that polymers can safely deliver therapeutic agents to the brain, there is laboratory data that other diseases may benefit from local delivery of pharmacologic agents; examples include dopamine for Parkinson's disease [26], nerve growth factor for dementia [27], papaverine for cerebral vasospasm [28], antibiotics for infection [29], and steroids for brain edema [30].

In conclusion, advances in imaging and surgical techniques have shifted treatments to earlier and safer interventions. Delivery of therapeutic agents to the brain is a critical challenge. Gliadel™ has demonstrated the 'proof of principle' that local sustained delivery of BCNU by polymer improves safety and survival. This approach may prove beneficial for vaccines and anti-angiogenesis therapy, as well as for other chemotherapeutic agents.

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