EDITORIAL

The Development of New Brain Tumor Therapy Utilizing the Local and Sustained Delivery of Chemotherapeutic Agents from Biodegradable Polymers

Henry Brem, M.D.
H. Christopher Lawson, B.S.

Department of Johns Hopkins University School of Medicine, Baltimore, Maryland.

In this issue of *Cancer*, Menei et al.[1] provide clinical evidence that a polymeric local delivery system is safe and may be beneficial in the treatment of patients with glioblastoma. Their findings indicate that 5-fluorouracil (5-FU), delivered locally by a biodegradable polymer (poly D,L, lactide-co-glycolide) [PLAGA]), can achieve appreciable levels in the cerebrospinal fluid (CSF) while maintaining a significantly lower concentration in the blood and producing limited systemic toxicity.

To our knowledge the antimetabolite, 5-FU, previously has not been used for adjuvant treatment after resection of malignant central nervous system tumors because of its need for systemic administration and its inability to cross the blood-brain barrier. However, delivering this agent intracranially circumvents the need for systemic delivery and limits toxicity. In addition, 5-FU is a radiosensitizing drug, which may enhance the effect of external beam radiation.

In a previous laboratory study, Menei et al.[2] utilized PLAGA, a biodegradable copolymer of glycolic and lactic acids, for the delivery of 5-FU into the rat brain. There was no evidence of toxicity and the agent was present in the microspheres for at least 12 days. The 5-FU-loaded PLAGA microspheres also were tested for efficacy. After receiving stereotactic intracranial injections of C6 rat glioma cells, rats treated with drug-loaded polymer had a significant prolongation of survival compared with rats treated with empty microspheres ($P = 0.017$).

The concept of utilizing biodegradable polymers to deliver chemotherapy has been established in the laboratory and clinic to treat malignant brain tumors. Biodegradable polymers comprised of the polyanhydride PCPP:SA were loaded with carmustine and implanted into the brains of rats, rabbits, and monkeys. Their distribution was studied and these polymers were shown to be biocompatible and efficacious against brain tumors.[3,4] Based on the foundation of these laboratory studies, a Phase I-II trial was completed that assessed the safety and dosage of these carmustine implants (Gliadel®;).[5] Twenty-one patients with recurrent malignant gliomas were treated with

Please see referenced original article on pages 324–9.

Dr. Brem is a consultant to Guilford Pharmaceuticals, Inc. and to Rhone-Poulenc Rorer, and Guilford has provided a gift for research in Dr. Brem's laboratory. The Johns Hopkins University and Dr. Brem own Guilford stock, the sale of which is subject to certain restrictions under University policy. The terms of this arrangement are being managed by the University in accordance with its conflict of interest policies.

Received April 5, 1999; accepted April 8, 1999.

Gliadel® wafer implants. Treatment was well tolerated in all patients and did not appear to produce systemic side effects.[5] The median survival after recurrence for the 1.9% loaded carmustine polymer wafer was 65 weeks; for the 3.8% loaded carmustine polymer wafer the median survival was 47 weeks, and for the highest dose, the 6.9% loaded carmustine polymer wafer, the median survival was 23 weeks. These results were encouraging and formed the basis of a Phase III, randomized, prospective, placebo-controlled, multiinstitutional trial to assess the efficacy of treatment against recurrent malignant brain tumors. In the 222 patients studied, the median survival was increased significantly in the treatment group from 23 weeks to 31 weeks ($P = 0.006$). In glioblastoma patients, the 6-month mortality rate was 44% for the treatment group and 64% for the placebo group ($P = 0.02$).[6] The results of this clinical trial led to the first Food and Drug Administration approval in 23 years of a new treatment for brain tumors. Gliadel® subsequently has been approved in Canada, South America, Israel, S. Korea and Europe.

Utilizing the principle that treatments that are beneficial at the time of disease recurrence should be even more effective at the time of initial therapy, we performed a Phase I, multiinstitutional trial at 3 institutions, comprising a total of 21 patients. We demonstrated that 3.8% loaded carmustine polymer implants were safe in combination with radiation therapy.[7]

Valtonen et al.[8] then performed a small, prospective, randomized, placebo-controlled study for the initial treatment of malignant gliomas. After surgical resection of their tumors, patients underwent intracranial placement of either carmustine-loaded polymers or empty polymer controls, as well as external beam radiation. The median survival in that study improved from 40 weeks for the placebo group to 58 weeks in the treatment group ($P = 0.012$). No other adjuvant therapies were utilized for these patients; at 2 years, 33% of the patients were alive in the treatment group compared with 6% in the control group. Three years after implantation, 25% of the patients in the treatment group were alive compared with 6% in the control group. A large-scale repeat study currently is underway in Europe, Israel, and the U. S. The results presented earlier form the basis for the use of Gliadel® in first-line surgery.

Numerous additional clinical studies with Gliadel® currently are underway. A dose escalation study has been sponsored jointly by the National Institutes of Health (NIH) and Guilford Pharmaceuticals, Inc. to evaluate the safety of carmustine polymer-loading doses from the clinically utilized 3.8% loading up to 28% loading.[9] A study sponsored by the NIH has been initiated to evaluate whether O^{6-}benzylguanine, a potent inhibitor of alkyltransferase (which inactivates carmustine), can be given concurrently with Gliadel® to reduce resistance to the drug. Combination chemotherapies with Gliadel® as well as the role of Gliadel® in treating patients with metastatic brain tumors currently are being evaluated through additional clinical trials. Newer drugs such as paclitaxel, doxorubicin, carboplatin, and 4-HC, as well as biologic agents such as cytokines and antiangiogenic agents, are being prepared in the laboratory for clinical trials.

The current study by Menei et al.[1] assesses the safety and distribution of 5-FU loaded into PLAGA microspheres. Eight patients with newly diagnosed glioblastomas received 5-FU-loaded PLAGA microspheres and external beam radiation after macroscopic total resection of their tumors. Sustained concentrations of 5-FU were found in the CSF for 1 month and the amount of 5-FU in the blood was small and transient. No side effects were appreciated at the lower treatment dose, but one patient treated at the higher dose developed cerebral edema. The median survival for this group of patients was 98 weeks, which is significantly higher than the historically reported median survival for patients with glioblastoma.[10]

This study is a promising initial step toward the development of a new treatment that may prove to be another weapon in our growing armamentarium of local therapies for combating malignant brain tumors. These microspheres could be introduced by stereotactic injection when surgical resection is not indicated. The development of this treatment would provide a new intracranial chemotherapeutic agent and radiosensitizer, as well as a new mechanism for local delivery. The current study should form the basis of a prospective, randomized study to evaluate the efficacy of 5-FU-loaded PLAGA microspheres in the treatment of patients with malignant gliomas.

REFERENCES

1. Menei P, Venier MC, Gamelin E, Saint-Andŕe JP, Hayek G, Jadaud E, et al. Local and sustained delivery of 5-fluorouracil from biodegradable microspheres for the radiosensitization of glioblastoma: a pilot study. *Cancer* 1999;86:324–9.
2. Menei P, Boisdron-Celle M, Croue A, Guy G, Benoit JP. Effect of stereotactic implantation of biodegradable 5-fluorouracil-loaded microspheres in healthy and C6 glioma-bearing rats. *Neurosurgery* 1996;39:117–24.
3. Fung LK, Ewend M, Sills A, Sipos EP, Thompson R, Watts M, et al. Pharmacokinetics of interstitial delivery of carmustine, 4-hydroperoxycyclophosphamide and paclitaxel from a biodegradable polymer implant in the monkey brain. *Cancer Res* 1998;58:672–84.
4. Tamargo RJ, Myseros JS, Epstein JI, Yang MB, Chasin M, Brem H. Interstitial chemotherapy of the 9L gliosarcoma: controlled release polymers for drug delivery in the brain. *Cancer Res* 1993;53:329–33.

5. Brem H, Mahley MS, Vick NA, Black KL, Schold SC, Eller TW, et al. Interstitial chemotherapy with drug polymer implants for the treatment of recurrent gliomas. *J Neurosurg* 1991;74:441–6.
6. Brem H, Piantadosi S, Burger PC, Walker M, Seiker R, Vick NA, et al. Placebo-controlled trial of safety and efficacy of intraoperative controlled delivery by biodegradable polymers of chemotherapy for recurrent glioma. *Lancet* 1995;345:1008–12.
7. Brem H, Ewend MG, Piantadosi S, Greenhoot J, Burger PC, Sisti M. The safety of interstitial chemotherapy with BCNU-loaded polymer followed by radiation therapy in the treatment of newly diagnosed malignant gliomas: Phase I trial. *J Neurooncol* 1995;26(2):111–23.
8. Valtonen S, Timonen U, Toivanen P, Kalimo H, Kivipelto L, Heiskanen O, et al. Interstitial chemotherapy with carmustine-loaded polymers for high-grade gliomas: a randomized double-blind study. *Neurosurgery* 1997;41:44–8.
9. Olivi A, Bruce J, Saris S, Engelhard H, Judy K, Kelly D, et al., for the NABTT CNS Consortium and Guilford Pharmaceuticals Inc. Phase I study of escalating doses of interstitial BCNU administered via wafer in patients with recurrent malignant glioma (MG). *Proc Am Soc Clin Oncol* 1998;17:387.
10. Kornblith PL, Walker M. Chemotherapy for malignant gliomas. *J Neurosurg* 1988;68:1–17.