Polymers to treat brain tumours

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Brain tumours are difficult to treat by conventional methods. A biodegradable polymer, poly-[bis(*p*-carboxyphenoxy)propane sebacic acid] with a nitrosourea, carmustine, has been demonstrated to be biocompatible in the brains of experimental animals and to release drugs in a predictable sustained manner. Carmustine impregnated in polymers appears to be more effective than when delivered by standard methods. A Phase I clinical study has demonstrated the safety of this approach in treating brain tumours and a Phase III placebo-controlled study is currently underway. Other applications of the polymer in the treatment of brain diseases are discussed.

Keywords: Drug delivery, polyanhydrides, biodegradation, carmustine

The median survival for a patient with a malignant glioma, regardless of the method of treatment, still remains < 1 yr after diagnosis[1]. Chemotherapy has slightly prolonged this survival, but at the price of systemic toxicity. Researchers therefore began to explore new approaches to the treatment of brain tumours based on their unique biological behaviour. Glioblastomas have been observed to be a localized disease, with 90% of malignant gliomas recurring within a 2 cm margin of the original tumour[2]. Indeed, local treatments, such as interstitial radiation therapy, have proven effective in prolonging life by delaying the local recurrence of the tumour[3]. The problem with interstitial radiation is the non-specificity of the cell-killing that occurs with high-dose local irradiation. The approach in the current research was therefore to develop methods of administering more-specific drugs that were generally not toxic and targeted at tumour cells.

There have been numerous attempts to deliver drugs locally in the brain. In 1963, Ommaya[4] used a subcutaneous reservoir attached to a catheter for sterile access through ventricular cerebral spinal fluid and tumour masses. Folkman *et al.*[5] were able to deliver low molecular weight anaesthetic agents through silicone rubber into the brain. Rosenbloom *et al.*[6] and Ueno *et al.*[7] reported using silicone to deliver chemotherapeutic agents. In 1987, Bouvier *et al.*[8] utilized direct delivery of medication in brain tumours through chronically implanted catheters. Diemath[9] has reported the experience of 269 patients with intraoperative placement of 50 mg of Methotrexate®. The problem with these systems is that they either involve permanent implants or do not protect the drug from degradation. To solve these problems, yet to achieve the goal of bypassing the blood-brain barrier thereby increasing the concentration of drugs in the brain and minimizing systemic exposure, the author sought a method for incorporating a drug into biodegradable polymers. Leong *et al.*[10] described features of poly-[bis(*p*-carboxyphenoxy) propane sebacic acid] that made this polymer particularly attractive as a candidate for treating brain tumours. They showed that polymers could be formulated to release drugs for periods of time ranging from days to years. Extreme hydrophobicity protected the drug from degradation. The polymers, which degrade by pure surface erosion, are available in wafers, sheets, rods or microspheres. They can be constructed with a wide range of physical properties from rigid to very flexible. Incorporation of drugs is simple, can be accomplished at low temperature and requires no solvents.

To determine whether the polyanhydrides would be appropriate to test the hypothesis that a controlled release of drugs in polymer would improve the treatment of brain tumours, a series of preclinical studies were proposed to determine: (1) the biocompatibility in the brains of rats, rabbits and monkeys, in the subcutaneous space in rats and in the corneas of rabbits, (2) drug distribution, by pharmacokinetic studies and autoradiography, and (3) effectiveness of systemic *versus* local therapy, followed by intracranial *versus* systemic therapy.

The biocompatibility studies in the rabbit and rat demonstrated that the polymer alone was well tolerated and minimally reactive. The amount of reactivity was similar to commonly utilized implants such as Gelfoam® and Surgicel®[11,12].

Monkey studies were then carried out to determine the safety of these implants in the cynomologous (macaca fascicularis) monkey brain. It was shown that they were similarly safe and were degraded completely within 3 month[13]. Kinetic studies demonstrated that local release of bis(2-chloroethyl)-1-nitrosourea (BCNU) in a polymer from the brain yielded very high sustained levels in the ipsilateral hemisphere for long periods of time. By contrast there were minimally detectable concentrations of BCNU in the blood and contralateral hemisphere only for the first day or two[14,15].

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A study was then carried out to show the intracranial effectiveness of the polymers[16-18]. Rats received intracranial implants of 9L gliomas; they then underwent reoperation for insertion of polymers. Some polymers contained BCNU and others were controls. Some rats received systemic chemotherapy. The tumours grew in a predictable fashion. All of the control animals were dead in 11 ±1 d. The systemic BCNU (intraperitoneal) treatment group had a mean survival of 27 ± 2 d and the BCNU-polymer group had a mean survival of 69 ± 10 d. Total regressions of tumour were only observed in the rats receiving active drug in the polymers. It was concluded from the preclinical studies that:

(1) Polymeric carriers were biocompatible with the brain.
(2) Polymeric carriers could release biologically active BCNU in a gradual controlled fashion.
(3) Interstitial delivery of antineoplastic drugs resulted in high drug levels restricted to the site of pathology.
(4) In the brain, interstitial chemotherapy bypassed the blood-brain barrier and might minimize systemic toxicity.
(5) Interstitial chemotherapy was more effective than systemic therapy in inhibiting tumour growth.

Based on these reports, a clinical study of interstitial chemotherapy for recurrent malignant astrocytomas using BCNU incorporated into biodegradable polymers was begun. The rationale for the clinical study was that the half-life of BCNU *in vivo* is approximately 12 min[19]. The polymer protected the BCNU from degradation. At the time of surgical resection, the cavity was covered with BCNU polymer; therefore, the target tumour cells were exposed directly to BCNU (*Figure 1*). Three doses of BCNU were utilized in polymers, with BCNU loading of 1.9%, 3.9% and 6.4%. The corresponding surface concentrations of BCNU/mm^2 were 25, 50 and 82.5 μg, respectively, and the total doses were 30, 60 and 100 mg. A total of 21 patients were entered into this study which was carried out at five medical institutions (Johns Hopkins University, Northwestern University, University of Alabama, Duke University and University of California Los Angeles)[20].

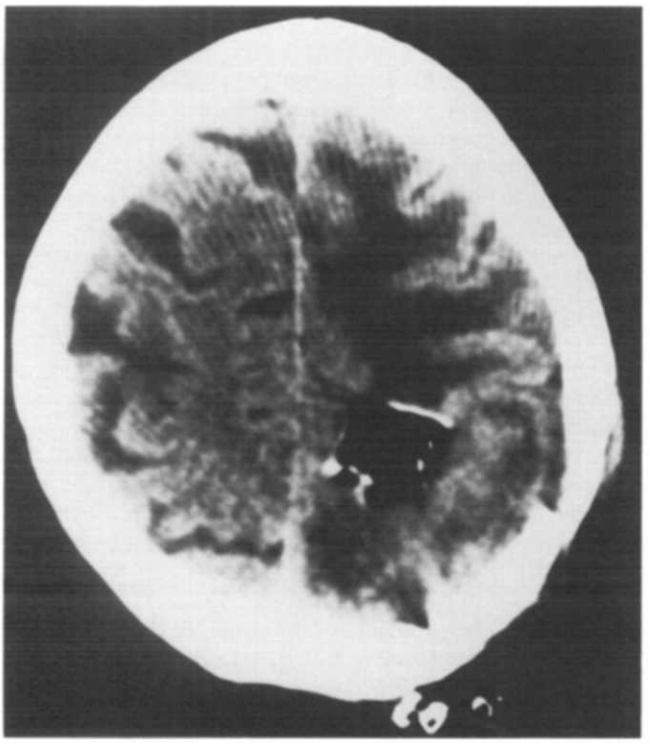

Figure 1 Computerized tomographic X-ray of a patient's brain 1 d after surgery. The bright white linear polymer discs are well visualized. Their degradation can be followed by sequential non-invasive radiological procedures. The polymer discs are placed along the brain surface (the black hole seen in the X-ray) from which the tumour was removed.

The study group had a mean age of 49 yr. Of the patients, 81% had glioblastomas; the remaining 19% had anaplastic astrocytomas. The overall post-implant mean survival was 49 wk; the overall survival from the time of diagnosis was 95 wk. Of interest, patients maintained excellent Karnofsky performance scores during the first 7 wk after implantation of polymer, demonstrating that they were fully functional. Based on the good results of this study, a prospective double blind, placebo-controlled study of BCNU delivered from a biodegradable, surgically-implanted polymer for treatment of recurrent malignant glioma is now under way at 16 medical centres across the USA and Canada.

While awaiting the results of the effectiveness of BCNU-polymer chemotherapy, other applications of the polymer for treating brain tumours are being developed. For example, it has now been demonstrated that polymers can release dexamethasone safely in the brain[21]. By using ethylene vinyl acetate copolymer, ipsilateral intracranial concentrations of 42 μg/g on the side of the implant can be achieved, with 0.68 μg/g in the contralateral hemisphere and 1.23 μg/g in the plasma[22]. When animals implanted with 9L glioma were treated with polymers implanted in the brain, they survived longer. Thus, dexamethasone can be effectively administered intracranially in a manner that releases high doses locally to those areas of the brain where control of oedema is necessary, with minimal exposure to the systemic circulation.

Other applications include implantation of polymers impregnated with heparin and cortisone and other angiogenesis inhibitors which have been shown to be effective against brain tumours[23]. Possible non-neoplastic applications of polymers for the brain include dopamine release for Parkinson's Disease[24,25] and Bethanechol® release for Alzheimer's Disease[26].

In conclusion, it was demonstrated that polymers can be utilized to release drugs in a controlled manner directly to the brain, bypassing the blood-brain barrier. Polymers have been shown to be a safe and effective means for releasing chemotherapeutic agents to treat brain tumours. Clinical safety in the human brain has been demonstrated. Clinical studies are under way to test the effectiveness of this approach with BCNU in patients in whom standard therapy has failed. Other uses of the polymer are currently being developed, with the hope that these new methods of controlled drug delivery will provide better ways to inhibit tumour growth.

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