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Local drug delivery

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Abstract

Intensive research efforts are now focused on the development of new strategies for more effective delivery of drugs to the central nervous system. These strategies include chemical modification of drugs, disruption of the blood–brain barrier, and utilization of alternative routes for drug delivery. This paper focuses on local drug delivery for the treatment of brain tumors. It reviews papers published in the past year on local chemotherapy and immunotherapy. Other aspects of local drug delivery are discussed, including convection-enhanced delivery and drug delivery via a controlled-release microchip.

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Local chemotherapy

Abbreviations:

O6-BG O^6-benzylguanine,

IUdR 5-iodo-2′-deoxyuridine,

pCPP:SA poly(carboxyphenoxypropane:sebacic acid),

PLGA poly (dl-lactide-co-glycolide

It is estimated that in 1999 brain tumors were diagnosed in 16,800 Americans and that 13,100 Americans died from these lesions [1]. Despite significant advances in imaging, neurosurgery, and radiation therapy, the prognosis for most patients remains dismal. Glioblastomas are considered among the most difficult neoplasms to treat, with a median survival of less than 1 year even after surgical resection, radiotherapy, and systemic chemotherapy [2–4]. Because most patients with glioblastomas have tumor recurrences within 2 cm of the original resection field [5], efforts to treat these patients have focused on local drug delivery. One strategy is to use implantable biodegradable polymers that release high concentrations of chemotherapeutic agents directly into the central nervous system [6–10]. This approach minimizes systemic toxicity and bypasses the restrictions of the blood–brain barrier.

A phase III prospective, randomized, double-blind, placebo-controlled study in patients with high-grade recurrent gliomas treated with 3.85% carmustine-impregnated polymers consisting of poly(carboxyphenoxypropane:sebacic acid) (pCPP:SA) has shown that polymer-delivered chemotherapy significantly improved survival [11]. In 1996, 3.85% carmustine-impregnated polymers (Gliadel, Guilford Pharmaceuticals, Baltimore, MD) received Food and Drug Administration approval for the treatment of recurrent malignant brain tumors. This was the first drug in 23 years to be approved by the Food and Drug Administration for treating brain tumors. Subsequently, regulatory agencies in Europe, Asia, and South America have approved Gliadel.

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Further characterization of interstitial carmustine for brain tumors

Studies of carmustine-impregnated polymers in the past year provided a more detailed analysis of the release characteristics of carmustine and focused on the chemical properties of the wafers during large-scale manufacture and storage. Although several previous studies reported on the distribution of chemotherapeutic agents in brain tissue, these studies were based on one-and two-dimensional models [12–15]. Wang *et al.*[16•] developed a three-dimensional simulation to study the effect of various factors on the delivery of carmustine to brain tumors. Systemic administration and controlled-release delivery from polymers were simulated using fluid dynamics software (Fluid Dynamics International, Inc., Evanston, IL) to predict the temporal and spatial variation of drug distribution. Delivery of carmustine by polymers provided a higher mean concentration and longer carmustine exposure time than did systemic administration. Using a surgical model, the authors predicted that implantation of a carmustine/ethylene-vinyl acetate copolymer matrix after resection of 80% of the tumor would be more effective than direct wafer implantation without surgical resection. The study provides a quantitative examination of the working principles of Gliadel wafers for the treatment of brain tumors.

Domb *et al.*[17] analyzed the chemical properties of carmustine-impregnated polymers during large-scale production and storage. They investigated the preparation of carmustine polymers under the Good Manufacturing Practice rules and regulations of the Food and Drug Administration, the release and polymer degradation properties, and the storage and irradiation stability of this implant. *In vitro,* carmustine was released constantly for the first 60 hours, with 100% release after 120 hours, at which time about 80% of the polymer was degraded [17]. In comparison, *in vivo* primate studies show prolonged release, with clinically significant levels of carmustine (0.1 to 7.5 μM) 1 to 2 cm from the polymer implant up to 30 days after polymer implantation [14]. Finally, Domb *et al.* [17] showed that the molecular weight of carmustine-impregnated wafers remained unchanged when stored at –20°C and that terminal sterilization with gamma-irradiation did not affect the release properties of the wafers.

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Biocompatibility of poly (dl-lactide-co-glycolide microspheres implanted into the brain

Before polymer-based drug delivery systems can be used in the brain, it is necessary to establish their safety. One bioerodible polymer that has a long and successful history of use as a suture material is poly (dl-lactide-co-glycolide) (PLGA) [18]. It has also been used for sustained systemic delivery of peptides and steroids [19–21]. Although preliminary studies have been performed to characterize the biocompatibility of PLGA microspheres in the brain [22,23], little is known about the short-and long-term astrocytic response to PLGA implants in the central nervous system. Emerich *et al.*[24] implanted PLGA microspheres stereotactically in the rat brain. They found no difference in glial fibrillary acidic protein reactivity between the polymer-implanted and control sides at time points ranging from 1 hour to 1 year after surgery. The majority of the PLGA polymers disappeared between 1 and 4 weeks postoperatively.

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Local delivery of radiosensitizers

One advantage of microspheres over polymer wafers is that they can be delivered stereotactically to deep-seated lesions in the brain that are not readily accessible by surgery. Their small size permits repeat implantation under local anesthesia. Drug-impregnated microspheres can also be injected into the walls of a surgical resection cavity. Recently, Menei *et al.*[25] incorporated the radiosensitizer 5-fluorouracil into biodegradable PLGA microspheres for the treatment of glioblastoma. 5-Fluorouracil was chosen for incorporation into biodegradable microspheres because it does not cross the blood–brain barrier and sustained release may improve its antitumor activity. Previous experiments in rats established the effectiveness of local delivery of 5-fluorouracil against malignant glioma.

On the basis of these animal studies, a phase I pilot study was performed in eight patients with primary glioblastoma [26•]. After surgical resection of the glioblastoma, 5-fluorouracil microspheres of two different doses (70 and 132 mg) were implanted into the resection cavity. External beam radiation

(59.4 Gy) was delivered within 7 days of surgery. Significant levels of 5-fluorouracil were found in the cerebrospinal fluid, whereas the levels in the blood were small and transitory. In one patient the postoperative course was complicated by recurrent brain swelling when 5-fluorouracil was delivered at the higher dose. Although the number of patients was limited, the overall median survival was 98 weeks from the time of implantation, with two long-term survivors of 139 and 153 weeks, respectively. The median survival of 98 weeks compares favorably with previous retrospective reviews in which the median survival was 50.6 weeks when patients with malignant brain tumors were treated with surgery and radiotherapy alone [27]. This study establishes the feasibility of delivering intratumoral 5-fluorouracil via biodegradable PLGA microspheres [28].

Other radiosensitizers, including 5-iodo-2′-deoxyuridine (IUdR) and 3-amino-1,2,4-benzotriazine 1,4-dioxide (tirapazamine) [29,30], have been assessed for local drug delivery in experimental brain tumor models. IUdR is a halogenated pyrimidine that competes with thymidine in the biosynthesis of DNA. Its effectiveness as a radiosensitizer increases with the percentage of thymidine replacement. Tirapazamine is most effective under hypoxic conditions, where it is reduced to yield a free-radical intermediate that results in DNA damage and cellular death [31]. Williams *et al.*[32,33] demonstrated that IUdR can be released effectively from pCPP:SA polymers both *in vivo* and *in vitro* for the treatment of experimental malignant gliomas. Using a U251 malignant flank glioma model in nude mice, Williams *et al.* showed that tumor volume was significantly reduced in the flanks of animals that received a combination of IUdR polymer and radiotherapy in comparison with control animals. Geze *et al.*[34] reported on the release of IUdR from PLGA microspheres. The incorporation of poly (d,l-lactide) oligomers into the PLGA matrix increased the overall *in vitro* drug release to a 6-week period, the standard time course of conventional radiation therapy. *Ex vivo* experiments with human brain tumor fragments and IUdR microspheres were performed. By use of immunohistochemistry, these experiments demonstrated IUdR incorporation into the nuclei of human brain tumor cells for up to 40 days after implantation.

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Local drug delivery for experimental brain metastases

Metastatic lesions to the central nervous system are more common than primary malignant brain tumors and have a poor prognosis. Current therapies, including surgery, conventional radiotherapy, and stereotactic radiosurgery, are limited in controlling intracranial metastases [35–37]. Breast carcinoma ranks second behind lung cancer as the most common cause of cancer metastases to the central nervous system. Approximately 10–20% of patients with metastatic breast cancer have intracranial disease [38]. Ewend *et al.*[39•] tested the effectiveness of interstitial chemotherapy and radiotherapy against an experimental animal model of intracranial breast cancer (EMT-6) delivered stereotactically to BALB/c mice. Locally delivered chemotherapy (20% carmustine in pCPP:SA polymers) improved survival over a placebo polymer, radiotherapy alone, or a combination of radiotherapy and a lower concentration of interstitial chemotherapy (10% carmustine). Locally delivered chemotherapy (20% carmustine) resulted in an improved survival rate of 70% at 200 days for a tumor that is uniformly fatal in this animal model. Mice receiving placebo polymer or radiotherapy alone had a median survival of 17 days and there were no survivors beyond 21 days. On the basis of these and other experimental studies [40], two multi-institutional clinical trials to study the use of carmustine-impregnated polymers for metastatic lesions are in progress.

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Clinical trials of carmustine-impregnated polymers

Newly reported developments in the laboratory have led to additional clinical trials for local drug delivery. Sipos *et al.*[41] report that escalating doses of carmustine delivered from pCPP:SA polymers improved survival in an experimental brain tumor model. A dose-response relationship for carmustine was observed. The two highest loading doses of carmustine (20% and 32%) improved survival 40-fold ($P < 0.001$). The 20% carmustine-loaded polymer achieved the best balance of toxicity and antitumor efficacy, yielding a 75% long-term survival rate in an otherwise uniformly fatal tumor model [41]. Further evaluation of 20% carmustine-loaded pCPP:SA polymer in primate brain suggests that high-dose

carmustine delivery may be achieved with acceptable toxicity [14]. Based on these findings the National Cancer Institute has funded a multi-institutional clinical trial evaluating up to 28% loading doses of these polymers. Preliminary results suggest that polymers loaded with up to 20% carmustine are well tolerated in patients who have undergone surgical resection of malignant glioma [42].

One limitation of chemotherapy is that many brain tumors become resistant to carmustine and other alkylating agents. This resistance may be due, in part, to a DNA repair protein found in a majority of brain tumors [43,44]. Recent reports suggest that O^6-benzylguanine (O^6-BG), an alkyltransferase inhibitor, enhances the efficacy of carmustine by inhibiting this DNA repair protein [45,46]. Because O^6-BG is believed to cross the blood–brain barrier, it could be hypothesized that the intravenous delivery of both O^6-BG and carmustine would reduce the resistance of the tumor. However, the difficulty with this approach is that even though O^6-BG is itself nontoxic, its presence will increase the systemic toxicity of intravenous carmustine (myelosuppression). To overcome this obstacle, interstitial carmustine may be delivered along with systemic O^6-BG. This approach will eliminate O^6-alkylguanine-DNA alkyltransferase activity in the human brain, increase the effectiveness of Gliadel, and reduce the risk of systemic toxicity. The National Cancer Institute is sponsoring a multi-institutional clinical trial to test this hypothesis clinically.

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Local immunotherapy

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Immunotherapy for brain tumors

Another approach to cancer therapy is the development of a treatment strategy that specifically targets tumor cells utilizing the host's immune system. Tumor vaccines rely on tumor cell antigens and costimulatory cytokines to enhance a host response. Several cytokines have demonstrated

an antitumor effect *in vivo,* including granulocyte-macrophage colony-stimulating factor [47], interleukin-2 [48], interleukin-4 [49], and interleukin-12 [50]. One cytokine of particular interest is interleukin-2, which is associated with the growth of cytotoxic T lymphocytes and the enhancement of natural killer/lymphokine-activated killer cells [51,52]. Early clinical studies focused on the systemic delivery of interleukin-2 for the treatment of metastatic melanoma and renal cell carcinoma. Although initial results appeared promising, systemic toxicity was significant [53].

One problem with systemic delivery of interleukin-2 is that this cytokine exerts its effects locally in a paracrine fashion. Most cytokines are produced in high concentrations at the site of the antigen, where they serve as the signal for the appropriate immune response. This paracrine element is lacking with systemic administration. An alternate approach for using cytokines to stimulate the immune system is to deliver them locally to the tumor in a sustained fashion. Local delivery produces high concentrations at the tumor site with negligible systemic toxicities and obviates passage through the blood–brain barrier. Animal experiments have shown that the intracranial production of interleukin-2 through genetically modified cells has a potent antitumor response that works in a paracrine fashion [47,54,55].

Recent papers described antitumor effects with the paracrine delivery of interleukin-4. Benedetti *et al.*[56•] showed that rat malignant gliomas could be eradicated by retroviral-mediated *in vivo* delivery of the interleukin-4 gene. In addition, a direct correlation between the amount of interleukin-4 at the tumor site and rat survival was found. Rats cured of intracranial glioma developed immunologic memory because they rejected a rechallenge of glioma cells implanted in the contralateral hemisphere. These results were corroborated by Saleh *et al.*[57], who showed that implantation of retroviral packaging cells producing an interleukin-4-containing retrovirus rapidly eradicated rat C6 cell gliomas and provided sustained protection against subsequent intracranial challenge [58•]. The antitumor effects of interleukin-4 were associated with infiltration of eosinophils, CD8+ cells, and the inhibition of angiogenesis.

Most studies of interleukin-2 and interleukin-4 delivery have used genetically engineered cells that secrete cytokines directly at the tumor site [59–62]. This approach is limited by the cost of producing such cells and the variability of cytokine production. Therefore, alternative delivery methods have been sought for the development of uniform tumor vaccines [63]. With newly developed techniques for protein delivery, recent reports have shown that interleukin-2 and -12 can be delivered by microspheres [64–66]. Early reports of cytokine delivery by microspheres appear promising. Interleukin-2 microspheres injected intracranially at the tumor site are highly effective in protecting animals challenged with fatal tumor doses in the 9L gliosarcoma model in rats and the B16-F10 melanoma model in mice. Animals treated with interleukin-2 microspheres statistically survived longer than animals treated with autologous tumor cells genetically engineered to secrete interleukin-2. The interleukin-2 microspheres also provide immunologic memory by protecting animals from a subsequent intracranial tumor challenge [67].

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Combination chemotherapy and immunotherapy for brain tumors

Intracranial chemotherapy cannot reach all residual tumor cells after surgical debulking in patients with malignant gliomas. Nevertheless, it may result in such significant cytoreduction that the immune system is equipped to eradicate the remaining tumor cells. Support for this hypothesis comes from experimental studies demonstrating that the curative potential of cytokine-secreting cells is limited to animals with relatively small tumors [68–70]. Based on these observations, Sampath *et al.*[71•] postulated that combined intracranial chemotherapy and immunotherapy would provide a synergistic antitumor response. The authors demonstrated that the combination of paracrine immunotherapy, via nonreplicating genetically engineered tumor cells that produce interleukin-2, and the local delivery of 10% carmustine polymers, produced a synergistic prolongation of survival in mice challenged intracranially with a lethal dose of B16F10 tumor cells. Histologic examination at day 14 of animals treated with combined chemoimmunotherapy revealed an acute and chronic inflammatory reaction

with a high density of polymorphonucleocytes, macrophages, and lymphocytes.

The use of interstitial chemotherapy in conjunction with intracranial immunotherapy is based on experimental evidence of increased antigenicity of tumors after exposure to cytotoxic drugs [72,73]. The release of intracellular antigens through the cytotoxic effect of chemotherapeutic agents is believed to increase the number of tumor peptide antigens and thus promote an inflammatory antitumor response [74]. By enhancing the intrinsic immunogenicity of the tumor, interleukin-2 immunotherapy is believed to bypass T-helper function [75] through the promotion of cytotoxic T lymphocytes and enhanced natural killer/lymphokine-activated killer cell activity [52,76]. This might be especially relevant in glioma patients, in whom T-cell function is thought to be suppressed [77].

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Other advances in local drug delivery

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Convection-enhanced delivery

Under normal physiologic conditions, brain interstitial fluid moves by both convection and diffusion. Unlike diffusion, convection (bulk flow) results from a pressure gradient and is independent of molecular weight [78,79]. Interstitial infusion into the white matter creates a pressure gradient that increases convection and can be used to efficiently deliver drugs to large regions of brain without significant functional or structural damage [80–82]. Using these principles, convection-enhanced delivery [83] allows for the homogeneous targeted delivery of high concentrations of macromolecules with a volume of distribution that is linearly proportional to the volume of infusion [81,84]. It has potential in the delivery of chemotherapeutic agents to surgically inaccessible brain tumors and ones located in eloquent regions of the brain. As has been previously shown with drug-impregnated polymers [85,86], it may have applications for the delivery of therapeutic agents to regions of the brain that are affected by

neurodegenerative diseases (*ie,* Parkinson disease, Alzheimer disease) [87]. Based on experimental brain tumor models [13,14], convection also plays a role when carmustine-impregnated polymers are used to treat brain tumors. This convection is believed to result from local cerebral edema, which produces an elevated pressure gradient between the brain interstitium and the ventricular space.

To determine what factors influence the optimization of convection-enhanced delivery, Chen *et al.*[88] delivered ^{14}C-albumin to the striatum of rats. They evaluated the effect of the rate of infusion, cannula size, concentration of the infusion, and preinfusion sealing time on convective delivery by using quantitative autoradiography. They found that the rate of infusion and cannula size significantly affected the convective distribution of the molecules. At low rates of infusion (0.1 and 0.5 μL/min), the infusate was contained at the target site. At higher rates of infusion (1.0 and 5.0 μL/min), however, the infusate leaked back along the cannula tract above the striatum because of increased fluid pressure. Although cannula size did not affect the volume of distribution, larger cannula size was associated with leakback, as increases in diameter facilitate the formation of a low-resistance pathway along the surface of the cannula [88].

In order for convection-enhanced delivery to be effective in the treatment of brain tumors, high drug concentrations must be maintained in the brain tissue for extended periods. In an effort to evaluate convection-enhanced delivery of a low-molecular-weight, water-soluble agent, Groothuis *et al.* [89] compared the delivery of ^{14}C-sucrose to rat brain by intravenous, intraventricular, and convection-enhanced intracerebral infusion using quantitative autoradiography. Intraventricular administration produced sucrose concentrations that decreased exponentially with distance away from the ventricular wall. Convection-enhanced delivery resulted in focal concentrations of sucrose up to 10,000 times higher than those concentrations in the intravenous group. The isotope pattern demonstrated a central component resulting from convection and a peripheral component resulting from diffusion. This study also showed that convection-enhanced delivery maintains high drug levels in brain tissue for prolonged periods.

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The microchip

The combination of polymer and microchip technology has resulted in a new approach to complex controlled drug delivery. Santini *et al.*[90••] reported on the development of a solid-state silicon microchip that can provide controlled release of single or multiple chemical substances at varying time points. Therapeutic agents (solid, liquid, or gel) are released after the electrochemical dissolution of a thin anode membrane covering the microreservoir. A microbattery, multiplexing circuitry, and memory can be integrated directly into the device, allowing it to be mounted on the tip of a small probe, implanted, or swallowed. This device may have implications for the treatment of brain tumors, especially for therapeutic agents that are synergistic but act over distinct time courses. With the proper selection of biocompatible device materials, this "pharmacy-on-a-chip" may have the potential to deliver up to 1000 different drugs on demand.

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Conclusions

Local drug delivery has significant clinical implications for the treatment of malignant brain tumors. It provides an effective means to bypass the blood–brain barrier, produces a high concentration of drug directly in the region of the tumor, and minimizes systemic toxicity. Clinical trials with carmustine-impregnated polymers have validated the hypothesis that local drug delivery can extend survival in patients with malignant brain tumors. New drug delivery strategies and therapeutic agents are being intensively explored to improve on these initial results. The release of chemotherapeutic agents, cytokines, and radiosensitizers from biodegradable polymers or microspheres has shown excellent potential in experimental models. Numerous clinical trials with local drug delivery and other therapeutic agents are ongoing in the hope of defining the best treatment strategy to improve patient survival. The development of new technologies such as the solid-state silicon microchip, immunotherapy, and convection-enhanced delivery holds great promise for the future.

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