Chapter 13

Interstitial Chemotherapy for Malignant Gliomas

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Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/62838

Abstract

Glioma is the most common primary tumor in the central nervous system (CNS). Even with aggressive treatments, gliomas remain as one of the most devastating tumors. Chemotherapy through oral administration of temozolomide (TMZ) is currently the standard regimen for malignant gliomas. However, the systemic toxicity and drug resistance are frequently observed in glioma patients. In order to improve the efficacy and minimize side effects, multiple strategies have been developed. Interstitial chemotherapy is a promising one. By directly delivering chemotherapeutic agents in tumor bed, interstitial chemotherapy bypasses the blood–brain barrier (BBB) and therefore achieves a higher concentration with less systemic exposure. In this chapter, we will have a thorough review on the development and the application of interstitial chemotherapy in gliomas, with the focus on the biomaterial-based and convection-enhanced delivery system. In addition, the future of interstitial chemotherapy is also be shortly discussed.

Keywords: malignant gliomas, local therapy, surgery, adjuvant chemotherapy, temozolomide, Gliadel waffer

1. Introduction

Malignant gliomas account for more than 50% of primary central nervous system (CNS) tumors and are among the most formidable cancers in human beings (1). Although aggressive debulking surgery followed by radiation and chemotherapy is the mainstay for malignant gliomas, the prognosis of malignant gliomas remains far from satisfactory. The 5-year overall survival (OS) is as low as 9.8% for patients with glioblastoma multiforme (GBM), a malignancy classified as grade IV by the world health organization (WHO) (2). The recurrence seems to be inevitable for malignant gliomas. Most patients with recurred GBM will die within 6 months even with salvage treatments.

The exact mechanisms underlying the intractability of malignant gliomas have not been fully understood, but the inherent resistance and the sheltering environment of brain have been proposed to protect the disease from conventional treatments. First of all, the infiltrative growth pattern of glioma cells makes the complete surgical resection almost impossible. Second, the existence of blood–brain barrier (BBB), which is tightly formed by capillary endothelial cells together with astrocytes, restricts the entry of most systemically administered chemotherapeutic agents into the tumor parenchyma (3). Third, the inherent and acquired insensitivity to radiation and chemotherapy through the disturbance of signaling pathway in glioma cells results in the resistance to current therapies (4). Because gliomas seldom metastasize outside the CNS and usually recur within 1–2 cm from the original tumor site, it is reasonable to expect the efficacy of directly delivering potent chemotherapeutic drugs into the tumor mass and its adjacent area. By this means, not only a higher drug concentration around the tumor but also a minimal systemic toxicity can be achieved.

2. Early experience

2.1. Topical application

Various methods have been attempted for locoregional therapy. The initial experience started with topical application. In 1963, Heppner and Diemath (5) treated brain tumor patients with local chemotherapy by placing gelatin sponges soaked with endoxan. Similarly, Ringkjob applied gelatin sponges filled with cytostatic agents including 5-fluorouracile (5-FU), methylene hydrazine, and thiophosphoramide to the resection cavity in patients with gliomas and brain metastases (6). Although the adverse effects were minimal in both studies, the clinical benefits were either hard to define or inappreciable. As a result, topical application of chemotherapeutics was gradually disregarded.

2.2. Direct injection

Direct injection is another early strategy to give local therapy. A subcutaneous reservoir (e.g., Ommaya reservoir) is implanted with its catheter into the resection cavity during surgery of brain tumors. Repeated injection of multiple chemotherapeutic agents can be done trough the reservoir postoperatively. Because direct injection is easy and repeatable, a number of studies have been done to explore the efficacy. In a Phase I/II trial, Boiardi et al. (7) implanted Ommaya reservoir in 12 patients with recurred malignant glioma. Two cycles of mitoxantrone were directly delivered into intratumoral cavity through Ommaya reservoir with or without systemic chemotherapy. The treatment was well tolerated in all patients. Either response or stable disease was found in 9 of 12 patients. A Japanese group investigated the histopathological changes after local chemotherapy via Ommaya reservoir (8). Massive coagulation necrosis surrounded by abundant reactive collagenous tissues, gliomesenchymal tissue, and infiltrating lymphocytes was found in the tumor bed, especially in areas around the catheter tip of Ommaya reservoir. This finding suggested the effectiveness of local chemotherapy. In

http://dx.doi.org/10.5772/62838

2008, Boiardi and colleagues (9) reported a non-randomized study with a large sample size. Two hundred and seventy-six patients with recurrent GBM were enrolled. Among them, 161 cases (Group A) were only treated systemically with oral temozolomide (TMZ), while 50 patients (Group B) were re-operated and received TMZ therapy postoperatively, and 50 cases (Group C) were treated with re-operation, postoperative TMZ, and locoregional therapy with mitoxantrone. The overall survival for Group C, B, and A was 27, 26, and 15.5 months, respectively ($p = 0.1$). The median survival after tumor recurrence was 16.8, 12, and 6.6 months for Group C, B, and A ($p = 0.001$), respectively. The authors therefore suggested that a second surgery combined with local chemotherapy would prolong the survival of patients with recurrent malignant gliomas.

In addition to chemotherapeutics, other agents have also been investigated for local therapy via direct injection. For example, Mamelak and colleagues (10) evaluated the safety and biodistribution of iodine-131 (^{131}I)-TM-601, a synthetic radioiodinated targeting peptide, for recurrent malignant gliomas in a Phase I trial. A total of 18 patients received a single dose of ^{131}I-TM-601 from one of the three dosing panels (0.25, 0.50, or 1.0 mg of TM-601). The agent was injected into the tumor cavity via a subcutaneous reservoir 2 weeks after surgery. The dosimetry analysis demonstrated a long-term retention of the agents around the injection site. The median half-life in the cavity margin was more than 50 h. No severe adverse effects were found during the delivery. Among 11 patients who completed the 180-day follow-up, two patients with recurrent GBM survived more than 30 months. The median survival was as long as 77.6 weeks in a subgroup of patients who received 0.5-mg dose of ^{131}I-TM-601. In another study, Prados and colleagues investigated the safety and efficacy of local gene therapy in recurrent GBM patients. Virus-producing cells (VPC) containing the herpes simplex virus thymidine-kinase (HSV-Tk) gene were injected into tumor cavity directly during debulking surgery and postoperatively via reservoir, followed by ganciclovir treatment (11). Among 30 patients enrolled in the study, 16 had severe adverse events such as infection, skin necrosis, and myelosuppression. The median survival of the series of 30 patients was 8.4 months. Six patients (20%) survived more than 1 year from the date of enrollment. The authors concluded that the direct delivery of gene therapy demonstrated some evidence of efficacy, while the improvement of procedures was needed to decrease the toxicity. Other studies also evaluated the feasibility to treat gliomas locally with immunotherapeutic agents such as autologous lymphocytes and immunomodulators (12, 13).

Although antecdotal reports of success achieved by direct injection of chemotherapeutics for glioma patients can be frequently found in literatures, no large-scale well-designed Phase III trial has been ever performed. In fact, local chemotherapy through direct injection has its own limitations. Firstly, repeated puncture and injection through the reservoir are associated with increased risk of intracranial infection and hemorrhage. Secondly, the injected drugs heterogeneously distribute in the tumor cavity through this approach. A sharp drug distribution gradient has been found, with an extremely high concentration around the tip of the catheter and a significant drop in the adjacent area. Therefore, the clinical exploration of local chemotherapy via direct injection dramatically declined.

3. Polymeric drug delivery

3.1. History

In order to overcome the drawbacks mentioned above and to achieve the local controlled release of chemotherapeutics, efforts have been made to develop delivery system with synthetic polymers. Early in 1970s, an ethylene vinylacetate copolymer (EVAc) was employed to generate a poriferous matrix and incorporate macromolecules such as chemotherapeutics (14). The impregnated agents are released from the matrix in a predictable and sustained style by diffusion. The rate of release depends on the physicochemical property of the agents, such as solubility, charge, and molecular weight. However, EVAc was restricted by the non-degradable nature and was therefore seldom used in neuro-oncology.

3.2. Carmustine implants

3.2.1. Background information

Various biodegradable polymers, such as the 1,3-bis(p-carboxyphenoxy) propane and sebacic acid (PCPP-SA), the fatty acid dimer sebacic acid (FAD-SA), and poly(lactide-co-glycolide) (PLGA) polymers, have been investigated in the last 3 decades. But until now, PCPP-SA is the most successful and widely used polymer for brain tumors. This compound has several advantages as matrix (15). Firstly, PCPP-SA is hydrophobic and can therefore protect the impregnated drug from inactivation by the surrounding aqueous environment. Secondly, the two-stage degradation of PCPP-SA matrix results in the gradual release of the content. At the first stage, the bonds between sebacic acid and sebacic acid or those between sebacic acid and CPP rapidly hydrolyzed, whereas the bonds between CPP and CPP take a longer time to degrade. This initial degradation is followed by a process of inward erosion which starts at the surface of the matrix and goes interiorly into the core. By modulating the ratio of sebacic acid and CPP in the matrix, the speed of degradation can be adjusted from hours to days as required. In addition, the breakdown of the PCPP-SA does not leave foreign body behind. Currently, the only US Food and Drug Administration (FDA) approved local chemotherapeutical agent for brain tumors, that is, Gliadel wafer, is composed by PCPP-SA as matrix and 1,3-bis(2-chloroethyl)-1-nitrosurea (carmustine or BCNU) as content.

BCNU is one of the most effective chemotherapeutics against malignant brain tumors at the time when the first local polymeric drug delivery system was being developed. BCNU is a classic alkylating and exerts its anti-tumor effect by forming inter-strand crosslink in DNA and subsequently inhibiting the replication and transcription of DNA in tumor cells (16). The highly lipid-soluble and nonpolar nature of BCNU makes it ideal for cancers in CNS because the agent has a good penetration of BBB. The concentration of BCNU in cerebral spinal fluid (CSF) is as high as 30% of that in plasma after intravenous injection. Clinical studies have demonstrated that systemic administration of BCNU is capable of prolonging the survival of patients with malignant gliomas (17). As a result, BCNU alone or combined with other agents has once been the most frequently used chemotherapy regimens for malignant gliomas. Although effective, intravenously administered BCNU is limited by its toxicities (18).

http://dx.doi.org/10.5772/62838

Gastrointestinal adverse effects such as nausea and vomiting can be observed shortly after infusion of BCNU and last for hours. Systemic BCNU therapy also causes myelosuppression. The peak of hematologic suppression may occur 1 month after BCNU administration, and it may take weeks for the recovery of bone marrow. In addition, pulmonary injury is another toxicity caused by BCNU treatment. Although rare, with the occurrence of approximately 5% of the patients, the BCNU-associated pneumonitis induces restrictive pulmonary disorders and subsequently progressive lung fibrosis, even after the withdrawal of the agent. Some patients terminate the chemotherapy due to the severe and irreversible toxicities. Based on its clinical efficacy against malignant brain tumors and the undesirable adverse effects, BCNU was impregnated into the PCPP-SA polymers. The BCNU wafers were explored for preclinical testing followed by clinical investigation.

3.2.2. Preclinical evidence

Preclinical exploration established the safety of the wafers in the CNS. Brem and colleagues (19) implanted the PCCP-SA polymers in the frontal lobe of rabbits and evaluated the biocompatibility. No neurological deficits or behavioral abnormalities suggestive of toxicity were observed. All the tested animals survived to the date of sacrifice. The histological analysis revealed that the inflammatory reaction from PCCP-SA was not significantly different from that in the controlled group implanted with Gelform, a widely used hemostatic material in neurosurgical operations. In primate models, the interstitial chemotherapy with BCNU polymers alone or combined with external beam radiation was found to be safe. The localized inflammatory response induced by BCNU wafers was well tolerated and manageable (20).

The *in vivo* experiments were also performed to evaluate the pharmacokinetics of BCNU wafers. In a rat model, the concentration of radiolabelled BCNU on the coronal sections of the brains was measured (21). BCNU delivered by polymers was at a concentration of 1 mM around the implanted site for the entire 30-day experiment. On day one, after implantation, BCNU penetrated the brain at a radius of 5 mm at a significant concentration, which was defined as 10% of the maximum concentration at the brain/polymer interface. Grossman and colleagues (22) investigated the intra-cerebral drug distribution in rabbits after the implantation of BCNU wafers. Radiolabeled BCNU was detected in 50% the area of the brain sections 3 days after BCNU-polymer implantation. On day seven, the concentration of BCNU was as high as 6 mM at the distance of 10 mm from the implantation site, which is far more than the active concentration of 14–16 μM against glioma cells *in vitro*. Because BCNU impregnated in polymers is released in a controlled manner, Fung and colleagues (23) calculated and compared the area under curve (AUC, concentration over time) of BCNU delivered by polymers to monkey brain and that administered by intravenous injection. In that study, polymeric BCNU delivery was estimated to achieve a 4-fold larger AUC in distant sites of brain and as high as 1200-fold more at the brain/polymer interface, in comparison with the conventional intravenous administration.

The efficacy of interstitial chemotherapy with BCNU was then tested in animal models. Tamargo and colleagues (24) demonstrated that local delivery of BCNU via polymers significantly prolonged the survival of rats intracranially implanted with 9 L gliosarcoma cells,

compared with intraperitonal injection of the agent. The median survival of animals treated with BCNU polymers was 62 days, which was more than double that for rats treated with systemic administration. In another study with the rat orthotopic glioma model, BCNU-impregnated polymers were found to be superior to extend the lifespan of tumor-bearing rats, compared with the direct injection of BCNU into the tumor tissues (25).

3.2.3. Clinical trials

The preclinical evidence of the safety and the effectiveness of polymeric BCNU delivery rationalized the investigation of the clinical benefit of this therapy. Brem and colleagues reported a multicenter Phase I–II trial with BCNU polymers in recurrent glioma patients. In that study, twenty-one patients with recurrent malignant glioma were enrolled (26). Up to 8 BCNU polymer wafers with three escalating concentrations, that is, 1.93, 3.85, and 6.35%, were implanted in the tumor beds. The authors demonstrated that the local treatment with BCNU was well tolerated, and no systemic adverse effects related to the therapy were observed in all patients. The study also recorded the survival outcome. The average survival time was 65, 64, and 32 weeks for patients treated with the low, medium, and high concentration of BCNU, respectively. Based on the result of this study, the further efficacy evaluation employed polymeric wafers with the 3.85% dose of BCNU. However, it is worth noting that patients treated with the highest dose of BCNU in the study had the shortest survival, which was not due to the adverse effects. In fact, the small sample size and the difference in the grade of gliomas among three groups account for the paradox. The group treated with the highest dose composed a higher proportion of GBM than the other two groups. In another multicenter single-arm Phase I trial, Brem and colleagues (27) demonstrated that the placement of polymeric BCNU wafers followed by the external radiation was safe for newly diagnosed malignant gliomas.

The role of interstitial chemotherapy with BCNU in recurrent malignant glioma was explored in a multicenter, double-blinded, placebo-controlled trial of 222 patients from 27 centers (28). Biodegradable polymers with 3.85% BCNU or empty polymer wafers were randomly implanted in the tumor site after resection. One hundred and ten patients received BCNU polymers and 112 had placebo-wafers. The median survival of patients with BCNU wafers was 31 weeks, which is superior to 23 weeks for patients with empty polymers (HR = 0.67, $p = 0.006$, after accounting for the effects of prognostic factors). Among 212 patients, 145 (65.3%) had pathologically confirmed GBM. Significantly reduced mortality at 6 months was observed in GBM patients treated with BCNU wafers (44%, 32 of 72 cases) than those treated with placebo implants (64%, 47 of 73 patients, $p = 0.02$). As a result, FDA approved the use of 3.85% BCNU wafers (Gliadel®) for recurrent malignant gliomas. However, a recent meta-analysis from the Cochrane library doubted the benefit of BCNU wafers in the treatment of recurrent malignant gliomas (29). No statistical difference in survival was found between patients treated with Gliadel® and those with placebo (HR = 0.83, 95% CI 0.62–1.10, $p = 0.2$). The acquired chemoresistant by the point of the implantation of BCNU wafers and the treatment-associated changes, such as the radiation-induced gliosis, which may restrict the

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diffusion of BCNU around the resection cavity, was suggested to be responsible for the ineffectiveness.

Efforts have also been put to investigate the efficacy of BCNU wafers as the initial treatment for newly diagnosed malignant gliomas. Two phase III multicenter, double-blinded, placebo-controlled trials drew the similar conclusions. In 1997, Valtonen and colleagues (30) published the study that was prematurely terminated due to the unavailability of the wafers. Thirty-two patients (16 in each group) with newly diagnosed malignant gliomas were randomly assigned to the active treatment group with BCNU wafers or the placebo group at the time of the primary surgery. An improved survival was observed in active treatment group (58.1 weeks), compared with the placebo group (39.9 weeks) ($p = 0.012$). For the subset of patients with GBM, BCNU wafers also offered survival benefit compared with placebo (53.3 vs. 39.9 weeks, $p = 0.008$). To confirm this positive result, a Phase III clinical trial with a larger sample size of 240 patients with newly diagnosed malignant glioma was subsequently performed (31). Patients randomly received the placement of either BCNU or empty polymers in the tumor bed, followed by the postoperative external radiation therapy. Prognostic factors, such as age, sex, Karnofsky performance status (KPS), and tumor grading, were balanced. The BCNU-treatment group had a significantly longer median survival (13.9 months) than placebo group (11.6 months) ($p = 0.03$). The risk of death was reduced by 29% in the treatment group. More adverse events including symptomatic intracranial hypertension (9.1 vs. 1.7%) and CSF leaking (5 vs. 0.8%) were observed in patients treated with BCNU wafers. In 2003, FDA granted the approval of Gliadel® wafers to treat newly diagnosed malignant gliomas. Until now, Gliadel® wafers are commercially available in the United States, Canada, Europe, and Japan for the adjuvant treatment of newly diagnosed malignant gliomas.

A preclinical works have revealed that the anti-glioma effect positively related to the loading dose of BCNU in biodegradable polymers in primate models (32). The question of whether a higher concentration of BCNU for interstitial chemotherapy is safe and capable of prolonging the overall survival of glioma patients was raised. The New Approaches to Brain Tumor Therapy (NABTT) CNS Consortium therefore investigated the safety of polymer wafers with higher concentrations of BCNU in a dose escalation trial (33). Forty-four patients with malignant gliomas were treated with polymer wafers containing BCNU at escalating doses of 6.5, 10, 14.5, 20, and 28%, respectively. The authors demonstrated that BCNU-impregnated wafers with a higher concentration of up to 20%, which was more than five times the dose of commercially available Gliadel®, were safe. The median OS of the patients after the placement of BCNU wafers was 251 days. Although further large-scale trials were suggested to explore the efficacy of high-dose BCNU wafers, the group has not initiated any of the studies. Recently, we evaluated the safety of high-dose BCNU-loaded biodegradable wafers in Chinese patients with recurrent malignant glioma (34). The wafers we used are comprised of poly (lactide-co-glycolide) (PLGA) containing 10% BCNU. PLGA is also a FDA approved material for drug delivery, which has more tunable mechanical properties and can be stored at 2–10°C in comparison with PCCP used in Gliadel®. In addition, PLGA degrades directly into water and carbon dioxide and does not need clearance in liver or kidney. The dosage of 10% BCNU is 2.5 times that of Gliadel®. Our study demonstrated that 12 implants with 240 mg

BCNU was well tolerated in tested patients. No dose-limiting toxicity was found. The median survival of this cohort of patients was 322 days. The 6-months, 1-year, and 2-year survival rates were 66.7, 40, and 13.3%, respectively. A registered double-blinded randomized Phase III trial is on-going to investigate the efficacy of the high-dose BCNU-impregnated PLGA wafers for recurrent malignant gliomas.

In 2005, Stupp and colleagues (35) published the milestone Phase III trial on the efficacy of adjuvant chemotherapy with temozolomide (TMZ) for GBMs. TMZ is a second generation alkylating agent, which can be administered orally. The Stupp regimen, that is, the concurrent chemoradiation with TMZ followed by six cycles of adjuvant TMZ, offered a modest but statistically significant extension of the survival of patients with GBM. As a result, TMZ is currently the standard-of-care for GBMs. The preclinical data presented by Plowman and colleagues (36) revealed that sequential administration of BCNU and TMZ resulted in a dramatic synergism and significantly inhibited the growth of glioma xenograft in mice. At the time when TMZ emerges, the safety profile and treatment outcome of TMZ with additional Gliadel® wafers was unclear. Gururangan and colleagues (37) investigated the safety of TMZ combined with BCNU wafers in a dose-escalation trial. Ten patients with recurrent malignant glioma were treated with BCNU implants followed by oral administration of TMZ at daily dose of 100, 150, and 200 mg/m^2, respectively. The combined treatment was well tolerated. Only one patient treated with TMZ at the highest daily dose of 200 mg/m^2 suffered from grade III thrombocytopenia. Until now, no randomized Phase III trial has been conducted to explore the efficacy of combined therapies in comparison with either TMZ or Gliadel® alone. Several prospective and retrospective studies with small number of patients indicated that sequential treatment with Gliadel® and TMZ resulted in an incremental gain of 2–3 months in median survival (38). Although the level of clinical evidence is not high enough, the combined treatment with Gliadel® and TMZ is currently recommended as an active option for newly diagnosed and recurrent malignant gliomas by the National Comprehensive Cancer Network (NCCN) guidelines (39).

3.2.4. Prevention for complications

The implantation of BCNU wafers is generally safe, but clinical lessons have been learned from the employment of Gliadel® for the management of malignant gliomas. The common adverse effects include healing abnormalities, seizures, and intracranial hypertension (40). Several strategies have been suggested to decrease the risks associated with BCNU implants (41). After the resection of the tumor, BCNU wafers should line up the surface of the tumor bed. Stack of the implants should be avoided because the stacking may result in an irregular release of BCNU due to the altered degradation kinetics of polymers. A large communication between resection cavity and ventricle is the contraindication for wafer implantation. The unexpected translocation of BCNU wafers into ventricle may lead to the life-threatening hydrocephalus. In addition, a watertight closure of the dura is critical to avoid CSF leak and decreases the risk of healing abnormalities and infection. Perioperative anti-convulsants are necessary to prevent seizures. Since the implantation of BCNU wafers is associated with

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increased risk of cerebral edema and intracranial hypertension, steroid is suggested to continue for at least 2 weeks after surgery.

3.2.5. Economic consideration

Although effective, BCNU wafers are expensive for the treatment of malignant gliomas. Much attention should be paid to the financial implication of the use of BCNU wafers. Rogers and colleagues (42) conducted a cost-utility analysis. The authors demonstrated that neurosurgery with Gliadel® implantation followed by radiation therapy costs 54,500 English pounds per additional quality-adjusted life-year (QALY) gained in comparison with surgery combined with radiotherapy alone. Probabilistic sensitivity model revealed a <10% probability that Gliadel® would be considered as cost-effective at a willingness-to-pay threshold of 30,000 English pounds per QALY. The authors concluded that Gliadel® is not cost-effective for healthcare resources but can be considered as an alternative adoption for the dreadful disease with a shortage of effective treatments.

3.2.6. Future prospects

Gliadel® represents the first success of the interstitial chemotherapy with biodegradable polymers. With the increased understanding of glioma biology and the advances in pharmaceutical technology, exploration of how to improve the efficacy of polymeric drug delivery is on the way. For example, O^6-alkylguanine-DNA alkyltransferase (AGT) is a well-known DNA repair protein, which protects tumor cells from damage through removing O^6-alkylguanine lesions introduced by alkylating agents such as BCNU and TMZ (43). Brain tumors, especially malignant gliomas, are rich in AGT. The level of AGT is negatively associated with the prognosis of patients with malignant glioma, who receive BCNU therapy (44). Therefore, the inhibition of AGT is a promising strategy to reverse the resistance of glioma cells to BCNU. Quinn and colleagues (45) reported the results of a Phase II trial to test the efficacy of the combination of O^6-benzylguanine (O^6-BG), an AGT inhibitor, with BCNU implantation. Fifty-two patients with recurrent malignant glioma were treated with infusion of O^6-BG and implantation of Gliadel® wafers. The median OS was 50.3 weeks, and the 1- and 2-year OS was 47 and 10% respectively, which suggested the potential clinical benefit. In addition, various chemotherapeutic agents other than BCNU have been exploited to deliver through polymeric system. Preclinical studies demonstrated that many drugs such as temozolomide, paclitaxel, taxotere, and camptothecin were efficacious against gliomas through polymeric delivery (46–49). Further clinical investigation of the safety and efficacy is therefore warranted.

4. Convection-enhanced delivery

4.1. Basic concepts

Convection-enhanced delivery (CED) is a catheter-based direct drug microperfusion technique, which was introduced by Bobo (50). CED continuously infuses soluble therapeutic

agents into targeted site in CNS through fine catheters implanted either by surgery or stereotaxis. The hydrostatic pressure gradient (bulk flow) in CED is generated through a motor-driven pump connected to the catheters. CED has several advantages as compared with other drug delivery methods. First of all, CED bypasses BBB and targets tumor bed through the implantation of catheters. The local concentration achieved by CED can be orders of magnitude higher than that produced via intravenous injection, while the systemic toxicity is minimal. Secondly, the pressure-driven CED creates a homogeneous distribution of infused agents in a large region in brain while the diffusion-driven drug delivery such as polymeric wafers usually leads to a limited penetration from the diffusive interface. A dramatic drop-off (250- to 1000-fold decrease) in concentration was observed with the polymeric delivery in the tissue 1–2 mm away from the surface (51). Thirdly, a very large volume of infusion can be achieved via CED. It has been demonstrated that a volume of 200 ml infusion into brain did not cause irreversible neurological deficits in patients with brain tumors (52). Finally, various agents with different molecular weights such as conventional chemotherapeutical drugs, small molecular inhibitors, and immunotoxins can be readily infused through CED. Whereas sophisticated technologies are required to integrate those agents into polymeric system.

4.2. Determining variables for infusate distribution

Several critical factors will influence the distribution of infusate delivered by CED. These include (i) infusion rate and volume; (ii) catheter features; (iii) anatomical structure and interstitial fluid pressure; (iv) intrinsic characteristics of infusate.

The concentration differential is the key driving force for diffusion-driven drug delivery such as polymeric chemotherapy. By contrast, CED is a method to deliver agents mainly dependent on pressure gradient in the interstitial space. As a result, the distribution volume of infusate is mainly determined by infusion volume and rate. In an animal model, the distribution volume correlates with infusion volume in a linear manner. However, this dependence of infusate distribution on volume of infusion disappears due to the infusate reflux along the catheter/brain interface (backflow) when the infusion rate reaches a threshold (e.g., >0.5 μl/min). Therefore, the optimal infusion rate and volume facilitate a better distribution of infusate.

Backflow is one of the major barriers for the clinical usage of CED. The reflux of infusate not only reduces the concentration of delivered drugs in the target location but also increases the risk of adverse effects such as chemical meningitis due to the leakage of the agents into the subarachoid spaces. The properties of the implanted catheters such as shape and size, and the implantation method of the catheters are associated with the incidence of backflow in CED. At the early stage of CED, the open-ended straight catheters were used, but the backflow was frequently observed even at a relatively low infusion rate. A systemic analysis demonstrated that the diameter of catheters positively correlates with the backflow (53). Catheters with the diameter of <1 mm significantly minimize the backflow and achieve better drug distribution (54). It has been suggested that a smaller size of the catheter introduces less tissue displacement and trauma, consequently reducing the backflow. Fiandaca and colleagues modified the shape of the catheter by developing a step design. The step catheter consists of 0.2 mm needle with a glued-in, internal silica tube (0.102-mm inner diameter) that extends beyond the end of

http://dx.doi.org/10.5772/62838

the needle by 5–10 mm (55). The authors demonstrated that the step catheter was reflux-resistant even when the infusion rate increased to as high as 5 μl/min. Gill and colleagues (56) evaluated the performance of CED with a recessed-step catheter, which incorporates an indwelling catheter with adjustable winged stop within a guide tube. This novel design showed a superior control of backflow in comparison with the conventional step catheter. Other catheter designs such as hollow fiber catheter, multiple port catheter, and balloon-tipped catheter have also been developed to minimize reflux and improve drug distribution (57).

The tissue structure and pathology at the targeting site are critical factors that influence the topography and the drug distribution achieved in CED. Normal brain tissues have significant heterogeneity and anisotropy in architecture and permeability for fluid flow. Anatomically, grey matter is mainly composed of glial cells and neuron somas, and the effective diffusivity is generally isotropic in grey matter. Whereas, white matter comprises bundles of axons connecting various grey matter areas to each other in brain. The permeability varies in white matter, primarily depending on the density and directional alignment of axon fibers (58). The diffusion of infusate is anisotropic in white matter. In addition, morphological analysis and mathematical models revealed that extracellular space is more easily extended by infusion fluid in white matter than that in grey matter (59, 60). As a result, white matter is more susceptible to extracellular bulk flow and infusate can travel a longer distance because of the higher permeability along the white matter. In pathological tissues such as gliomas, the bulk flow can be less predictable due to the heterogeneous cytoarchitecture and the treatment-related changes. GBM is characterized with the thriving growth of tumor cells, pseudopalisading necrosis, and glomeruloid vascular proliferation in histology (61). Interstitial fluid pressure (IFP) has been found to increase in intracranial tumors in preclinical models and patients (62). The leaky vasculature coupled with the resistance to bulk flow in the tortuous interstitial space of the surrounding grey and white matter is suggested to be the underlying mechanism for the increased IFP in GBMs (63). More importantly, IFP varies in different areas of the tumor. IFP elevates in the tumor center and dramatically drops toward the tumor periphery or the surrounding normal brain tissue. The outward pressure gradient restrains infusate to enter the tumor core, and the leaky tumor vasculature facilitates the rapid efflux of infused drugs into systemic circulation. Treatment-induced changes may also complicate the drug delivery in CED. For example, postoperative inflammatory reaction decreases the diffusion of drug with a larger molecular weight in extracellular spaces (64). In addition, to treat a residue tumor surrounding the resection cavity, which directly communicates with the subarachnoid space or ventricle, makes it more difficult to deliver drugs via CED. The numbers and placement of catheters should be carefully planned according to the postoperative tumor characteristics.

Besides, the intrinsic features such as the physical and chemical properties of infusate are highly related to the efficiency of CED. Drugs with small molecular weight can be employed in CED, but their faster clearance from CNS limits their diffusion. Agents that easily cross the BBB are not good choices for CED because they can be readily eliminated from the CNS and transported into the systemic circulation. Similarly, drugs that are rapidly taken up or metabolized in the CNS may reduce the distribution of the infusates. Viscosity is also an

important factor for bulk flow in CED. Intuitively, the less viscous the infusate is, the more smoothly it diffuses in the extracellular space. Subsequently, a larger diffusion volume is expected from the low-viscosity drugs. However, Mardor and colleagues (65) demonstrated in a rat model that agents with high viscosity tend to have an increased volume of diffusion because they are more resistant to backflow. Therefore, when a drug is chosen as a candidate for CED, its physico-chemical characteristics such as molecular weight, viscosity, clearance rate should be taken into account. In addition, novel strategies are explored to improve the efficacy of CED through delaying the degradation or clearance of agents in the target sites. To achieve this goal, drugs are conjugated or encapsuled with nanoparticles or liposomes (66, 67).

4.3. Agents for convection-enhanced delivery

A wide range of therapeutic agents, such as conventional chemotherapies, targeted toxins, viruses and oligonucleotides, have been investigated on CED for the safety and efficacy in the treatment for gliomas in clinical trials.

4.3.1. Conventional chemotherapeutics

Topotecan, a topoisomerase I inhibitor, is an ideal conventional chemotherapeutic agent for CED. Firstly, topotecan is more readily to accumulate in gliomas than in normal brain tissue. Secondly, it specifically kills glioma cells and is less toxic to normal brain. In addition, topoisomerase I is a natural-product agent with a high molecular weight. As a result, topotecan is difficult to bypass BBB when administered intravenously. Whereas topotecan is less easily removed into systemic circulation and can be retained in the targeted site for a prolonged time when it is infused via CED. Jeffery and colleagues conducted a Phase Ib trial to deliver topotecan to recurrent malignant gliomas (68). Sixteen patients were enrolled in that dose-escalation trial. The treatment was well tolerated with the stable maintenance of quality of life and neurocognitive functioning of patients. Tumors substantially regressed without significant systemic and neurocognitive adverse effects in selected patients with recurrent malignant gliomas refractory to conventional treatment. The total response of the single topotecan infusion was 69%. The results were encouraging for relapse patients in whom previous treatment had failed, but the efficacy of this treatment requires to be confirmed in Phase II and III trials.

Another conventional chemotherapeutic agent, paclitaxel, has also been delivered through CED to treat malignant gliomas. In a Phase I/II trial, a total of 20 cycles of intratumoral CED of paclitaxel was administered to 15 patients with histologically confirmed recurrent GBM (69). Among these 15 patients, complete response was observed in five cases and partial response in six cases, respectively. The response rate reached 73%. The poor response seemed to be associated with the backflow of paclitaxel into subarachnoid spaces, ventricles, and resection cavities. Although effective, the local delivery of paclitaxel caused significant incidence of complications including transient chemical meningitis in six patients, infection in three patients and transient neurological deficits in four patients. The treatment-related side effects have been suggested to be the results of infusate reflux. Strategies such as sealing the burr hole

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with bone wax and adapting the concentration of paclitaxel were used to prevent the extracranial leakage of the cytotoxic drug and minimize the treatment-induced side effects (70).

4.3.2. Targeted cytotoxins

Targeted cytotoxins represent a novel class of agents with high specificity for brain tumors. The potent protein toxins produced by bacteria are conjugated to carrier ligands, which specifically bind to the receptors on the surface of glioma cells. Less resistance to targeted cytotoxins was observed in glioma cells because the agents kill glioma cells through irreversible *de novo* protein synthesis, independent of any malignancy-associated genetic alterations. The relatively small molecular weight and the highly soluble proteinaceous nature of targeted cytotoxins make them attractive for CED.

TF-CRM107 is the first targeted cytotoxin investigated in clinical trials. The agent is composed of diphtheria toxin conjugated to transferrin-C and preferentially targets glioma cells due to the increased expression of transferrin receptor in tumor tissue. Preclinical works demonstrated that TF-CRM107 eliminated glioma cells at picomolar concentrations *in vitro* and significantly inhibited the growth of subcutaneous glioma xenografts in a mouse model (71, 72). Delivery of TF-CRM107 through CED was safe for patients with malignant brain tumors. In a dose-escalating trial, the treatment was well tolerated (52). No significant neurological and systemic adverse events were observed. In the subsequent Phase II trial, 44 patients with refractory and recurrent malignant gliomas were enrolled (73). TF-CRM107 (concentration of 0.67 μg/ml) was delivered continuously through CED at a rate escalating up to 0.2 ml/h per catheter (a total of 0.4 ml/h for 2 catheters) until a volume of 40 ml was infused. The outcome was encouraging, with a total response of 35% and a median survival of 37 weeks. Unfortunately, the multicenter Phase III trial failed to confirm the efficacy of TF-CRM107 delivered by CED. The study was stopped because an intermediate futility analysis revealed that the chance of positive outcome was <20%.

Cintredekin besudotox (CB, also known as also known as IL13-PE38QQR), a recombinant chimera protein consisted of IL-13 coupled with a truncated form of *Pseudomonas* exotoxin (PE38QQR), is one of the most well-studied targeted toxins. The toxicity and safety profile were carefully reviewed by Kunwar and colleagues (74). Fifty-one patients with recurrent malignant glioma including 46 GBMs, who were infused with CB via CED after resection, were evaluated. The treatment was well tolerated, and the adverse effects were mostly transient and manageable. The authors categorized the adverse effects according to the onset time related to the procedures including the placement of catheters and delivery of the agents. Three symptomatic periods were defined: The first one was between surgery and CED; the second was during CED and up to 7 days after infusion; and the third period was 2–10 weeks after treatment. Adverse events including intracranial hemorrhage and infection were more likely observed in the first period, which was related to the placement of catheters. Whereas the mass effect due to the volume of infusion was responsible for neurological deficits during the second period. Neurological deficits were also found in patients during the third symptomatic period. It has been suggested that the treatment-induced inflammation or the non-specific toxicity for normal brain cells resulted in the side effects. This study not only confirmed the safety of the

delivery of CB via CED but also provided important information about the pathophysiological mechanism underlying the adverse events observed in the clinical trial with CED, which is helpful to minimize the complications in further studies. A multicenter Phase III trial (Phase III Randomized Evaluation of CED of IL13-PE38QQR Compared to Gliadel® Wafer with Survival End Point in GBM Patients at First Recurrence, PRECISE) investigated the efficacy of CB infused via CED (75). Two hundred ninety-six patients with recurrent GBM were randomized to receive CED of CB or Gliadel® wafers. Unfortunately, although there was statistically significant improvement in progression-free survival between patients treated with CB and those with Gliadel® wafers (17.7 vs. 11.4 weeks, $p = 0.0008$), no survival benefit was found, with the median survival of 11.3 months for CB and 10 months for Gliadel® wafers for the efficacy evaluable population ($p = 0.310$). But it is worth noting that 32% of catheter placements were not performed per protocol specifications and drug distribution was not evaluated with image monitoring. These two limitations may be possible explanation for the failure of the trial. Lately, Sampson and colleagues (76) retrospectively analyzed the catheter positioning and drug distribution in the PRECISE trial using BrainLAB iPlan Flow software that was not available during the trial. The study demonstrated that more than 50% of catheters did not meet all positioning criteria among 174 cases with sufficient data. In addition, the simulation analysis revealed that the average coverage volume was very low, with only 20.1% of the 2-cm penumbra surrounding the resection cavity covered on average. Therefore, lessons learned from PRECISE trial clearly indicate that the accurate catheter positioning and the real-time monitoring of drug distribution are critical for the success of interstitial drug delivery via CED.

4.3.3. Future prospects

Until now, many other agents such as monoclonal antibodies (e.g., ^{131}I-chTNT-1/B mAb), oligonucleotides (e.g., TGF-beta2 antisense oligonucleotides) and viruses (e.g. LSFV-IL12) have been investigated via CED in early-stage clinical studies (77–79) and demonstrated benefit in selected patients. Well-designed randomized trials are required to confirm the efficacy. In the future, so as to fulfill an effective treatment strategy, CED will require optimized infusates, improved catheters, standardization of catheter placement, mathematical models to predict drug distribution, as well as the real-time monitoring of infusate delivery.

5. Conclusion

Malignant glioma, especially GBM, is still a devastating cancer in CNS. Despite of intensive treatment with neurosurgical resection, radiotherapy, and adjuvant chemotherapy with TMZ, the median survival is less than 2 years. Development of novel strategies against malignant gliomas is of urgent necessity. The advent of interstitial chemotherapy has definitely increased treatment options for patients with malignant glioma. Local delivery of chemotherapeutic agents bypasses the physiological barrier of normal brain, achieving a significantly increased concentration in targeted sites and a minimized systemic toxicity. Gliadel® wafers represent the success of interstitial chemotherapy for malignant gliomas. On the other hand, CED is a promising approach for local drug delivery, but improvement in the techniques is

http://dx.doi.org/10.5772/62838

required. In addition, novel methods such as micro-chips and gene delivery is under investigation (80). In a word, interstitial chemotherapy conveys the opportunity of more efficiently and effectively delivering anti-glioma agents to the infiltrative tumors than conventional routes of administration.

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