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Interstitial chemotherapy for malignant glioma: Future prospects in the era of multimodal therapy

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Abstract

The advent of interstitial chemotherapy has significantly increased therapeutic options for patients with malignant glioma. Interstitial chemotherapy can deliver high concentrations of chemotherapeutic agents, directly at the site of the brain tumor while bypassing systemic toxicities. Gliadel, a locally implanted polymer that releases the alkylating agent carmustine, given alone and in combination with various other antitumor and resistance modifying therapies, has significantly increased the median survival for patients with malignant glioma. Convection enhanced delivery, a technique used to directly infuse drugs into brain tissue, has shown promise for the delivery of immunotoxins, monoclonal antibodies, and chemotherapeutic agents. Preclinical studies include delivery of chemotherapeutic and immunomodulating agents by polymer and microchips. Interstitial chemotherapy was shown to maximize local efficacy and is an important strategy for the efficacy of any multimodal approach.

Key Words: Carmustine, Gliadel®, glioblastoma multiforme, interstitial chemotherapy, malignant glioma

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INTRODUCTION

The introduction of interstitial chemotherapy has dramatically changed the therapeutic and prognostic prospects of patients with malignant glioma (MG). The main features of MGs, which include the World Health Organization (WHO) Grade III gliomas (anaplastic astrocytoma, AA) and Grade IV gliomas (glioblastoma multiforme, GBM), are an aggressive growth pattern, their refractory nature, and an especially poor prognosis. MGs are locally aggressive within the central nervous system (CNS), and very rarely metastasize to other locations.[41,69]

Due to their invasiveness and high proliferation ratio, as shown by histological and clinical evidence,[25,37] the complete surgical resection of a MG mass, even when supported by intraoperative magnetic resonance imaging (iMRI), only has limited beneficial impact on patient survival.[41] The efficacy of postoperative adjuvant therapies on the residual tumor cells is undermined by the unique anatomical environment surrounding the brain and the tumor-related physio-anatomic barriers within the brain.[1]

Interstitial chemotherapy delivers localized administration of drugs using polymer implants directly at the site of the brain tumor. As such, interstitial chemotherapy plays a crucial role in the context of present and future multimodal approaches to MG.[46] Since the completion of randomized trials demonstrating the value of

Gliadel® (biodegradable polymeric wafers that deliver carmustine), temozolomide (TMZ) has been shown to induce responses in recurrent high-grade glioma and to improve median survival and results in relatively longer-term survival when used in the initial management of newly diagnosed patients.[24,62,70] Nonetheless, the combination with local implantation of carmustine-loaded wafers, which is capable of boosting survival, forms an essential part of the treatment for this disease, especially considering its extraordinarily poor prognosis.

Maximal therapy for patients with MGs consists of surgical debulking followed by multimodal therapy approaches with radiation therapy and a combination of systemic and local chemotherapy. This had led to a 9-month improvement in survival resulting in 19.8–21.5 months median survival.[38]

GLIADEL®: CLINICAL EXPERIENCE

Carmustine, or BCNU 1-3-bis (2-chloroethyl)-1-nitrosourea effect, is mediated by its chloroethyl moieties, which can alkylate reactive sites on nucleoproteins[72] and interfere with DNA synthesis and repair.[67] This agent forms intrastrand crosslinks in DNA, thus impairing DNA transcription and replication[29] (the high alkylating activity of BCNU is also the cause of its main side effect, interstitial pneumonitis, due to DNA injury to the alveolar lining cells[68] and suppression of hematopoiesis.[35] Another mechanism of activity is the carbamoylation of nucleoprotein lysine residues, with subsequent decrease in RNA and protein synthesis.

After both oral and intravenous administration, BCNU has a very short life, with the parent drug not being detectable after 5 min[42] and its active metabolites being detected in urine up to 72 h after the initial dose. Systemic delivery of this drug is associated with hematopoetic suppression (leukopenia, thrombocytopenia), pulmonary toxicity (pulmonary fibrosis), hepatic toxicity, and renal failure, with low levels resulting in the brain.[72] The local delivery of carmustine makes it possible to have a peak of approximately 19.4 ng/mL BCNU 3 h after Gliadel® insertion, which is lower than 1/600 of the peak BCNU level recorded after intravenous injections. Its levels decrease to less than the detection limit (2.00 ng/mL) after 24 h.[44]

The polymer currently used in patients is composed of polyanhydride poly[1,3-bis (carboxyphenoxy) propane-co-sebacic-acid] (PCPP-SA) and incorporates the chemotherapeutic drug, carmustine.[8-10] In earlier studies, other types of materials were examined for polymeric design, including ethylene-vinyl acetate copolymer (EVAc),[59,60] fatty acid dimer-sebacic acid (FAD-SA) copolymer, poly (lactide-co-glycolide) polymers or microspheres,[62] and poly (lactide-co-glycolide) nanospheres, among others.[18,19,50] These different types of polymers have different abilities to incorporate a variety of drugs. Polymers composed of EVAc have been used to incorporate carmustine;[21,22] FAD-SA have been used for hydrophilic drugs, such as carboplatin;[43] and poly (lactide-co-glycolide) for larger molecular weight compounds, such as 5-fluorouracil.[39] Despite these varying biomaterials, only Gliadel®, BCNU-impregnated pCPP-SA, has been used in patients.[8-10,62,70]

Interstitial chemotherapy with Gliadel® has been shown in randomized trials to improve outcome when used either as multimodality initial therapy in patients with newly diagnosed MG[62,70] or as an adjunct to surgery for recurrence.[8,70]

Interstitial chemotherapy via sustained-released polymer wafer involves the implantation in the surgical cavity of chemotherapeutic drugs loaded in biodegradable polymers. After implantation into the surgical cavity, the wafers undergo a constant degradation, thereby providing a sustained release of drug into the tumor cavity and surrounding brain parenchyma. These drug-impregnated polymers bypass the blood–brain barrier and are able to achieve high local chemotherapeutic concentrations, while minimizing systemic toxicity. Unlike local delivery, systemic administration of drugs requires long distance transport of higher systemic drug levels; hence, it entails more toxicity, and a significant portion of the drug is degraded before reaching its target site.[8-10]

In 1987, a Phase I/II clinical trial was conducted to identify the best-tolerated carmustine dose, where carmustine doses of 1.9%, 3.8%, and 6.4% per weight were used, and there were no significant side effects in any of the dosing groups. The median survival was 65, 64, and 32 weeks for the 1.9%, 3.8%, and 6.4% concentration groups, respectively. Because of the increased survival at 3.8% concentration as compared with 6.4%, a carmustine dose of 3.8% was selected for further clinical trials.[9] However, in 2003, a dose-escalation clinical study was conducted to evaluate higher concentrations of carmustine in patients with MGs.[44] Polymers with 6.5%, 10%, 14.5%, 20%, and 28% carmustine, by weight, were assessed, and the maximum tolerated dose was 20% (approximately five times the standard dose) without an increase in side effects.[44] Furthermore, the serum level of BCNU at the highest concentration of 20% serum was 27 ng/mL at 4 h. Regardless, the standard carmustine concentration remains 3.8% by weight.

The first randomized efficacy trial was conducted in patients with recurrent MGs. In this Phase III study of 222 patients from 27 institutions, patients were randomized to receive carmustine wafers impregnated with either 3.8% carmustine or no carmustine.[10] The median survival for the carmustine wafer cohort was 31 weeks as compared with 23 weeks for the placebo cohort ($P = 0.006$). Following Food and Drug Administration (FDA) approval

for recurrent MGs, carmustine wafers were also tested in newly diagnosed MGs.[62,70,71] In a Phase III study that was prematurely stopped because of lack of access to the wafers, 32 patients (16 per group) with newly diagnosed MGs were randomized to receive carmustine wafers or empty wafers.[29] The treatment group had a significantly longer median survival compared with the placebo group (58.1 vs. 39.9 weeks).[62] A larger Phase III clinical trial of 240 total patients was subsequently conducted. The median survival for the treatment group was significantly longer than the placebo group (13.9 vs. 11.6 months).[70,71]

GLIADEL: COMBINATION STUDIES WITH RADIOTHERAPY AND SYSTEMIC TEMOZOLOMIDE

More recently, the survival advantage of carmustine wafers in combination with radiotherapy and systemic TMZ was validated in retrospective, multiinstitutional French and Japanese studies for both newly diagnosed and recurrent MGs.[15,40] The French retrospective study showed improved survival compared with the Phase III, reporting a median survival of 16 months for newly diagnosed MGs and 7 months for recurrent MGs. This study also demonstrated the impact of total and subtotal resection on survival for both *de novo* and recurrent MGs and demonstrated that the combination of Gliadel® and radiochemotherapy with TMZ was well tolerated and could increase survival without increasing adverse events (AEs).[42] Another retrospective study carried out in Japan proved comparable to those of previous studies in the United States and Europe. The study showed overall survival rates of 100.0% and 68.8% at 12 and 24 months, and a progression-free survival rate of 62.5% at 12 months in newly diagnosed MGs and of 37.5% at 6 months in recurrent MGs.[2] The wafers in this study were shown to be safe with no AEs.

Another recent study, conducted prospectively and multicentrically on 92 cases, reported a median of 10.5 months progression-free survival and a median of 18.8 months of overall survival.[15] This study further confirms that the multimodal treatment of implanted carmustine chemotherapy and concomitant radiochemotherapy with TMZ yield better survival rates than those where carmustine or TMZ are used alone and independently from one another.[15] Another study conducted in the United Kingdom showed that multimodal treatment with carmustine wafers was associated with a median survival of 15.3 months.[3]

GLIADEL: COMBINATION STUDIES WITH OTHER CHEMOTHERAPEUTIC AGENTS

The efficacy of the Gliadel® implantation has been investigated in combination with both local and systemic chemo-immunotherapy. The combination of Gliadel® and permanent I-125 Seeds was addressed in four different clinical trials enrolling recurrent MG patients. The combination, apart from radiation necrosis (seen in up to 24% of the patients), was safe and resulted in favorable overall survival compared with Gliadel® monotherapy.[6,14,74] In the most recent study, conducted on a small subset of 17 patients with recurrent glioblastoma, the concomitant treatment of local iodine-125 and Gliadel® yielded an overall survival rate higher than Gliadel® alone (60 vs. 31 weeks).[28]

Gliadel® and radiation have safely been combined with various systemic chemotherapeutic agents, such as carboplatin in a Phase I trial on patients newly diagnosed with MGs[34]); PVC (procarbazine, lomustine, and vincristine) chemotherapy in newly diagnosed patients with MG in the context of a Phase I/II clinical trial;[32] and multiagent chemotherapy (TMZ, CCNU, CPT-11).[51] Gliadel® was also explored in combination with intravenous irinotecan,[52] and was reported to be well tolerated and possibly more effective than monotherapy in patients with recurrent GBM.

The tumor's ability to develop resistance mechanisms has been another obstacle for chemotherapeutic agents to overcome. One manner of resistance is the over-expression of O6-alkylguanine-DNA alkyltransferase (AGT), which protects the tumor from the mutagenic and toxic lesions induced by the BCNU. To obviate this, Gliadel® in combination with systemic delivery of O6-benzylguanine (O6BG), an inactivator of AGT able to suppress the AGT activity, has been investigated.[17,23] The initial trial of O6BG in patients with brain tumors demonstrated suppression of AGT activity when O6BG was administered at a dose of 120 mg/m^2 18 h before surgery[23] This study was followed by a Phase I trial of Gliadel® combined with a well-tolerated concentration of O6BG administrated as a 120 mg/m^2 bolus 1 h before surgery as well as by continuous infusion at 30 mg/m^2/day for up to 7 days.[66] The Phase II clinical trial of Gliadel® plus O6BG in recurrent GBM patients showed an 80% 6-month survival with 47 weeks median survival; A significant improvement compared with Gliadel® alone, which had a median survival of 56% 6-month survival and 31 weeks.[6,47]

FUTURE PROSPECTS

Interstitial chemotherapy, besides playing an important role in a regimen of radio and multi-agent chemotherapy, holds significant promise in emerging radio-immunotherapy strategies.

The relationship between the immunosuppressive effect of MGs and tumor progression as well as patient survival has been established.[21] As yet, immunomodulating

agents such as IL2 have only been evaluated in combination with BCNU in animal models. The combination of IL2 and BCNU, both locally delivered, has shown higher survival compared with those animals that received either one of the two drugs alone or the placebo implants.[50] However, recently, in a Phase I study, BCNU wafer implants combined with Dendritic Cell vaccination was shown to be safe and feasible with only one grade 3 AEs.[73]

The use of bevacizumab was recently approved by the FDA as second line in monotherapy for recurrent glioblastoma and, in Japan, for newly diagnosed glioblastoma. This is evidence of the wide recognition of the crucial role of antiangiogenic agents in the treatment of MGs. In this view, some preclinical studies deserve particular mention. One set of studies has shown the efficacy of local delivery of bevacizumab either alone or in combination with radiation and TMZ.[20] Other studies indicate that an antiangiogenetic agent, minocycline, originally used for its antibiotic effects, may be used as an effective antitumor agent when locally delivered.[7] Minocycline has also been shown to have a synergistic effect in combination with BCNU, resulting in significant extension of the median survival (82%) compared with BCNU alone ($P < 0.0001$) in an animal model of glioma.[16] This study, similarly to many other promising preclinical animal models, is further evidence that intracranially implanted polymers can successfully deliver various chemotherapeutic agents.

Interestingly, preclinical animal studies have shown polymers impregnated with TMZ have a significantly extended median survival as compared with oral TMZ[11] and improved efficacy with the combination of TMZ polymer, BCNU polymer, and radiotherapy.[49] As shown in multiple preclinical studies in animal models, the efficacy of BCNU and TMZ-impregnated polymers are representative of the effectiveness of the multimodal approach of interstitial chemotherapy.

ALTERNATIVE STRATEGIES

Convection-enhanced drug delivery

Convection-enhanced drug delivery (CED) is an alternative local drug delivery technique for the treatment of MGs. Since CED was introduced by Bobo *et al*., in 1994,[5] CED has evolved greatly and been part of several clinical trials.

Several key factors affect the distribution of solutes delivered using CED, including infusion rate, cannula shape and size, infusion volume, interstitial fluid pressure, particle characteristics, and tumor tissue structure.[48] Data from animal studies have shown that CED allows for uniform distribution of infusate covering distances of up to 3 cm from the site of catheter placement.[5]

However, the distribution of solutes becomes more complex within the brain of patients with MGs due to the effects that surgery, edema and leakage of drug into the subarachnoid space have on the tissue pressure gradients.[54] The advent of computer models and algorithms that predict drug distribution, the development of new catheter designs and the utilization of tracer models and nanocarriers have led investigators to refine and improve this delivery method.[54,55]

Recent clinical trials using CED for treating MGs have involved the delivery of different agents. These agents include: Targeted immunotoxins,[4,22] such as Tf-CRM107 and mutated forms of Pseudomonas exotoxin combined with IL-4; IL-13 ligands and EGFR-binding ligands; iodine-labeled chimeric monoclonal antibodies, such as Cotara®; and systemic chemotherapeutic agents, such as topotecan, carboplatin, and paclitaxel. Paclitaxel has shown to have acceptable safety profiles in Phase I/II clinical trials and, currently, recruitment for dose-escalation analysis for Phase III clinical trials is underway.[45]

TP-38 is a recombinant chimeric targeted toxin containing the EGFR binding ligand, transforming growth factor alpha (TGF-α), and a genetically engineered form of the Pseudomonas exotoxin, called PE-3n8. In 2001, a Phase I/II clinical trial examined the toxicity and response of TP-38 delivered by CED and revealed an acceptable safety profile.[53] The overall median survival after TP-38 was 23 weeks (range: 1.1–83.1 weeks). The median survival for patients with residual disease was 18.7 weeks, whereas those without radiographic evidence of residual disease had a median survival of 32.9 weeks.[53] A subsequent Phase III trial was planned, but has not yet opened.

Another targeting toxin delivered via CED is Tf-CRM107, a mutant diphtheria toxin linked to transferrin.[64] A Phase III study was conducted on Tf-CRM107, also known as TransMID, in 40 centers in the USA and Europe, but later aborted because an intermediate analysis showed less than 20% chance of positive outcome.

Interleukin-4-Pseudomonas exotoxin chimeric fusion protein, IL-4 (38-37)-PE-38KDEL also called cpIL4-PE or IL-4 cytotoxin, has demonstrated cytotoxic effects on glioma cells due to inhibition of cell proliferation, regulation of adhesion molecules, and induction of signal transduction through the JAK/STAT pathway.[26] IL-4 cytotoxin was successfully examined with a multicenter dose-escalation Phase I/II trial and showed an increase in overall median survival in 31 patients with recurrent MG.[65] Currently, another multicenter Phase II is in progress using the same fusion protein.[36]

Particularly interesting are the studies of the protein containing IL13 and the comparison study with Gliadel®. Three Phase I clinical trials were performed

using cintredekin besudotox (CB), a protein containing IL-13 combined with a truncated form of Pseudomonas exotoxin (PE38QQR) delivered via CED.[30] This was followed by MRI to check the catheter position, which allowed for the optimization of the catheter placement and assessment of the safety of CB.[54,56] Next, a Phase III randomized evaluation of convection-enhanced delivery of IL13-PE38QQR with survival end point (PRECISE) trial, which involved 52 centers in North America, Europe, and Israel, compared the efficacy of IL13-PE38QQR with Gliadel® wafers in patients with first-occurrence resectable glioblastoma.[31] CB demonstrated longer progression-free survival (17.7 vs. 11.4 weeks; $P = 0.008$). However, there was no significant improvement in median survival (36.4 weeks with CB, compared with 35.3 with Gliadel®), hence CB was not determined to be superior to Gliadel® wafers. Importantly, however, this study was found to be statistically powered to show a 50% improvement in survival compared with Gliadel® (despite the fact that no new therapy has ever shown more than a 25% improvement in this disease). Therefore the relative comparability of CB to Gliadel® was not considered a statistically valid conclusion and the study failed to provide sufficient support for US FDA approval of CB.[4,31]

CB has also been evaluated in newly diagnosed MGs. A Phase I clinical trial with CB, following radiation therapy with and without TMZ, demonstrated that CB combined with standard radiochemotherapy was well tolerated in patients with newly diagnosed GBM.[63]

Other systemically administered chemotherapeutics have also been evaluated for use by CED. A Phase I/II clinical study using CED of paclitaxel to recurrent gliomas showed, despite the positive response rate, significant complications associated with the intratumoral delivery of paclitaxel, including chemical meningitis, infections, and neurological deterioration.[33] In recurrent MGs a Phase I dose escalation trial on topotecan delivered by CED demonstrated a median survival of 45 weeks and a median time to progression of 20 weeks. A multicenter Phase II trial is planned.[12]

Convection-enhanced delivery is an excellent option for the local chemotherapy of inoperable brainstem gliomas. This was most recently shown in a study investigating the delivery of carboplatin via CED in an experimental brainstem animal model.[61] Currently, there are clinical trials underway of the CED delivery of carboplatin for the treatment of recurrent glioma and the CED delivery of another promising agent, 124I-8H9, for the treatment of diffuse intrinsic pontine glioma [clinical trials: NCT01502917 NCT01644955].

Microchips

Convection-enhanced delivery has demonstrated that broad distribution has great potential, but is also limited by uncertain spatial distribution and serious side effects. Microchips – miniaturized depot devices – are a viable method of controlled delivery of drugs in brain cancer, and could achieve a broad aggregate distribution profile.[13,57,58] These devices are capable of delivering multiple drugs with independent drug release profiles following a single implantation procedure.

There are two types of microchips – active and passive microchips. Active microchips allow precise temporal control over release kinetics and are designed by utilizing microelectromechanical systems (MEMS) technology combined with an activation mechanism based on thermally induced membrane failure.[13] In an experimental study an orthotopic glioma model compared the effects of drug release rates and timing with active microchips loaded with TMZ, and showed that early and rapid delivery of TMZ from the devices resulted in longest animal survival.[58]

The microchips with passive mechanism of release are the PLLA and liquid crystal polymer (LCP) microchips, produced from poly(L-lactic) acid (PLLA) and from LCP, respectively. PLLA consists of biodegradable polymers; LCP is nonbiodegradable but is biocompatible. An experimental study conducted in an orthotopic glioma model using both PLLA and LCP microchips loaded with TMZ demonstrated that intracranial TMZ delivery via microchips was more effective than TMZ systemic administration.[58]

An experimental study using a glioma flank model and investigated the effects of release of BCNU from LCP microchips and demonstrated that the sustained release of BCNU from the microchip was able to inhibit tumor growth. Interestingly, the drug remained intact in the microchip for much longer than in the polymer.[27] Additionally, microchips allow for a larger payload of drug than the drug–polymer mix. Also, microchips showed a more controlled and slower release of drug as compared to polymers, which, especially in acidic tumor environments, degrade more rapidly and uncontrollably than do microchips.[27,58] Due to these advancements the future application of microchip devices for intracranial chemotherapy holds a tremendous potential for the treatment of MGs.

CONCLUSION

Gliadel® wafers represent an innovative and safe way of delivering chemotherapy directly to intracerebral MGs. Building on the known activity of BCNU as an alkylating agent in MGs, this method allows for drug release in a constant and safe manner in the surrounding brain tissue. Clinical trials using Gliadel® have shown that it is a valid option in patients with either newly diagnosed or recurrent MGs. Several multimodal therapies, multichemotherapy, and chemo-immunotherapy are

currently at different stages of investigation. Interstitial chemotherapy, due to its unique properties, maximizes local efficacy and will long remain an important yardstick for the efficacy of any multimodal approach.

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