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Improving the delivery of therapeutic agents to CNS neoplasms: a clinical review

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1. ABSTRACT

Even though nearly thirty-years of clinical research has attempted to improve the outcomes for patients with central nervous system neoplasms, the survival remains limited for a majority of these patients. Diverse intracellular signaling pathways involving apoptosis, invasion, angiogenesis and relevant mechanisms of resistance associated with CNS neoplasms are continuing to be elucidated. Phase I and II studies of systemically delivered chemotherapeutic agents and biological agents targeting these pathways have largely resulted in modest outcomes. Although the functional blood brain barrier was identified nearly eighty years ago only recently has the complexity and relevance of the blood brain-tumor barrier (BTB) been recognized as an important factor that limits the effective treatment of CNS neoplasms. Several groups have focused their efforts at improving the delivery of therapeutic agents across the blood brain-tumor barrier. The purpose of the article is to review novel methods that have attempted to improve the delivery of therapeutic agents into the CNS for the treatment of CNS neoplasm.

2. INTRODUCTION

Several decades of intense research aimed at the treatment of gliomas (anaplastic gliomas and glioblastoma multiforme) and metastatic disease to the CNS has resulted in minimal improvements in outcomes for these patients (1-2). Although a large amount of resources has been invested in the discovery and identification of active chemotherapeutic agents, the ability of any agent to effectively control and eradicate neoplasms within the CNS is limited by the blood brain-tumor barrier (BTB). Our group, as well as others, have attempted to improve the survival of patients with CNS neoplasms by altering the permeability of the BTB or altogether circumventing the BTB by innovative means including: intra-carotid administration of chemotherapy, hyperosmotic agents to alter BBB permeability, vasoactive agents to selectively alter BTB permeability, chemotherapy impregnated wafers to increase local concentration of chemotherapy, direct intra-cerebral micro-infusion of tumor specific agents and instillation of monoclonal antibodies into a surgically created resection cavity (3-9)

3. INTRA-CAROTID ADMINSTRATION OF CHEMOTHERAPY, HYPERTONIC BBB DISRUPTION AND PHARMACOLOGIC MANIPULATION OF THE BTB

3.1. Intra-carotid delivery of Chemotherapy

Nitrosoureas (BCNU, CCNU, ACNU) have a broad tissue distribution, can penetrate the blood brain barrier and as a result they are considered one of the most active class of agents in the treatment of CNS neoplasms (10). As a result of the wide tissue distribution of nitrosoureas, intravenous administration results in considerable systemic toxicity. Common and serious toxicities associated with this class of agents included cumulative myelosuppression, renal toxicity, hepato-toxicity and pulmonary toxicity. There are several characteristics of nitrosoureas that make them attractive for intra-carotid delivery: 1) the high octanol/water coefficient, 2) short half life, 3) pre-clinical studies suggested that the activity of a nitrosoureas could be increased if it was delivered by the intra-carotid route as compared to the intra-venous route (11). Intra-carotid administration of chemotherapy could decrease systemic toxicities associated with intravenously administered nitrosoureas.

Hochberg (1985) evaluated 79 patients with malignant glioma that were treated with intra-carotid BCNU. Patients were treated at tumor recurrence, adjuvant or in the neo-adjuvant setting. Patients received one of several dose levels of BCNU from 240 mg/m^2 to a maximum of 600 mg/m^2 every 5-6 weeks (see Table 1). Patients who were treated via infra-ophthalmic carotid artery infusion at tumor recurrence survived 54 additional weeks (92 weeks after initial diagnosis). Patients who were treated with BCNU immediately after initial irradiation therapy survived 64 weeks (infra-ophthalmic carotid artery infusion) and 49.5 weeks (supra-ophthalmic carotid artery infusion). Of the 12 patients that received intra-carotid BCNU at tumor recurrence 11 patients survived 1 year from their recurrence. Ocular toxicity (ocular pain/retinal infarction/transient decreased visual acuity) was observed. Although there were nearly 3x the number of infra-opthalmic infusion of intra-carotid BCNU as compared to surpra-opthalmic infusions of intra-carotid BCNU, there was substantially less ocular toxicity if therapy was administered above the ophthalmic artery. Patients treated at tumor recurrence appeared to have an increase in survival as compared to patients that received intra-carotid BCNU in the adjuvant setting (3).

The CNS toxicity and lack of efficacy associated with the intra-carotid delivery of nitrosoureas in phase II studies (12) lead to the evaluation of less lipophilic though "active" agents or combinations of agents (carboplatin, cisplatin, bleomycin , etoposide, TNF-alpha) delivered by the intra-carotid route for the treatment of malignant glioma (13-17). Reports of CNS toxicity (ototoxicity/ocular toxicity) continued to accumulate in association with the intra-carotid delivery of these hydrophilic agents and phase II studies continued to show lack of improvement in survival (18-19). Even though higher concentrations of these small, hydrophilic agents reached the intravascular compartment of the CNS neoplasms due to the first-pass effect, the ability of the BBB/BTB to limit the entry of chemotherapy into tumor tissue remained an important obstacle. In an effort to increase the delivery of intra-carotid chemotherapy attempts were made to alter the permeability of the BBB either by global blood brain barrier disruption or by selective blood brain/tumor barrier disruption.

3.2. Blood brain barrier disruption by hypertonic agents

The use of hypertonic agents, such as mannitol alters the integrity of the endothelial cells by displacing the intracellular water from endothelial cell into the vasculature. This "shrinks" the endothelial cells which alters the integrity of the tight junctions and zona occludens connecting these endothelial cells. This results in the entry of chemotherapy into the interstitial space of the CNS by the paracellular route.

Doolittle (2000) reported the safety and efficacy of intra-arterial delivered chemotherapy in association with hyperosmotic blood brain barrier disruption in 221 patients diagnosed with CNS neoplasm of varying histologies (primary central nervous system lymphoma, primitive neural ectodermal tumor, germ cell tumor, low and high grade glioma and metastatic CNS tumor, brain stem glioma, optic nerve glioma, central neurocytoma, chloroma and pinocytoma). This multi-institutional study performed a total of 2,464 intra-carotid treatments with 89.4% of these treatments including hyperosmotic BBB disruption. Thirty-three percent of these patients were diagnosed with glioblastoma, 25% had primary central nervous system lymphoma and 14% had either grade II or grade III gliomas. A third of all patients had received prior chemotherapy, and 44% of patients had received prior radiation therapy. The treatment schema is described in Table 2. The objective response rates for patients with glioblastoma multiforme, primary CNS lymphoma and either grade II or grade III gliomas was 21%, 90% and 64% respectively. The response rates of phase II studies evaluating systemically delivery vincristine/methotrexate/procarbazine for the treatment of primary CNS lymphoma is comparable (20) to those reported by Doolittle 2000. Overall survival and time to progression was not reported. Three patients expired related to brain herniation. The pre-treatment of patients with seizure medication improve the previous reported incidence of seizures from 6% to 0% in this study. The addition of sodium thiosulfate (STS) diminished the incidence of high frequency hearing loss associated with the use of intra-carotid carboplatin.

Response rates for recurrent GBM are comparable in patients that have been treated with oral or intravenous chemotherapy including tamoxifen and procarbazine, thalidomide, interferon- β, cis-retinoic acid alone or in combination with temozolomide (21-25). As a result of the global alteration in BBB permeability and the frequent toxicities (see Table 3) associated with hyperosmotic BBBD other groups have attempted to *selectively* alter the permeability of BBB/BTB in anatomic areas involved with the CNS neoplasm.

Table 1. Intra-arterial BCNU for Glioblastoma Multiforme-Dose Levels and Stratum

Salvage Therapy	Adjuvant	Neo-Adjuvant
(N) BCNU dose q 5-6 weeks	(N) BCNU dose q 5-6 weeks	(N) BCNU dose q 4 weeks
3 250 mg/m^2	43 240 mg/m^2	6 240 mg/m^2 2
3 350 mg/m^2		
3 450 mg/m^2		
3 600 mg/m^2		
18 240 mg/m^2 1		

[1] Administered into the supra-opthalmic portion of the internal carotid artery, [2] If patients experienced tumor progression patients went immediately to radiation therapy.

Table 2. Hyper-osmotic Blood Brain Barrier Disruption treatment Schema

Pre-medication treatment regimen
• Intra-venous hydration: D51/2 NS x 6 hours
• Administer anti-epileptic agent
• Atropine
• Warmed 25% Mannitol-Administered 4-10 ml/second for 30 seconds
Chemotherapy regimen [1]
• Histology: Primative neural-ectodermal tumor, glioma, brain metastases
• Carboplatin [2] (Intra-arterial) 330mg/m2 day 1 and 2 Carboplatin administered 10 minutes after mannitol infusion
• Etoposide [3] (Intra-venous) 200mg/m2 day and 2
• Histology: Primary CNS Lymphoma, Brain stem glioma
• Methotrexate [4] (Intra-arterial) 2.5 gram day 1 and 2. 5 minutes after administration of mannitol infusion
• Cyclophosphamide (Intra-arterial) 500 mg/m2 day 1 and 2. 10 minutes after administration of mannitol
• Cycle repeated every 28 days

[1] Days 3-9 patients receive GCSF (granululocyte colony stimulating factor) until ANC (absolute neutrophil count) > 1000 for both regimens, [2] Post-medication: Sodium thiosulfate used as an oto-protective agent, [3] Formulation of etoposide changed, [4] Leucovurine rescue, Adapted from Reference 4

Table 3. Common Toxicities Associated with Intra-arterial adminstration of chemotherapy with or without hyperosmostic blood brain barrier disruption

Central Nervous System (CNS) Toxicity
• Headache
• Seizure
• High Frequency Hearing Loss
• Leukoencephalopathy
• Ocular Toxicity
• Brain Herniation
• CNS parenchymal damage
• Carotid dissection

3.3. Blood Brain/Tumor Barrier Disruption by Pharmacologic Manipulation

Several vaso-active molecules such as bradykinin, labradimil (bradykinin analogue), leukotrienes, as well as others have been identified as molecules that *selectively* alter BTB permeability. These agents represent a class of small molecule activators that alter BTB permeability by increasing vesicular transport. In preclinical studies it was determined that use of these agents activate the bradykinin-2 receptor or down stream molecules including nitric oxide, cGMP, potassium dependant calcium channels found on the vascular endothelium and/or the tumor. Activation of this cascade can improve delivery of various sized agents to tumors located within the CNS.

The most extensively studied vaso-active molecules in humans is the bradykinin analogue, labradimil. Both of these vaso-active molecules are peptides and as such have relatively short half-lives in the circulatory system. Pre-clinical studies have indicated that the effectiveness of labradimil at increasing BTB permeability is concentration dependent. To take advantage of the first-past effect, labradimil has been administered by the intra-carotid route. Intra-carotid administration improves the ability of low dose labradimil (300 ng/kg) to increase chemotherapy delivery within the CNS. For the treatment of malignant gliomas, intra-carotid labradimil has been evaluated in one phase I study, and intra-venous labradimil has been evaluated in two phase I studies for the treatment of malignant gliomas, one for adults and one for children (5, 26, 27). Two phase II studies assessing the efficacy of intravenous low dose labradimil have been performed in adults (28, 29).

Intra-carotid delivered labradimil (300 ng/kg) significantly increased the delivery of a radioactive tracer into brain tumors in patients with recurrent malignant gliomas (30) (see Figure 1 and Figure 2). This was shown using PET to measure uptake of the tracer ^{68}Ga-EDTA into tumor tissue. Little or no uptake was seen in normal brain tissue. Cloughsey (1999) performed a dose escalation study of labradimil plus carboplatin in a small group of patients with recurrent malignant glioma. Patients were given intra-carotid labradimil at a starting dose of 10 ng/kg combined with intra-carotid carboplatin at a dose of 100 mg. During the study, two patients had received carboplatin up to a dose of 600 mg. The dose of labradimil was escalated from the starting dose of 10 ng/kg to 30, 100 and 300 ng/kg. Patients were subsequently enrolled in the next dose level if there were no grade 3 irreversible toxicity or grade 4 toxicity in a minimum of two deliveries in at least two patients. Five patients had glioblastoma multiforme, five patients had anaplastic astrocytoma and five patients had anaplastic oligoastrocytomas. Most patients had previously received chemotherapy that included procarbazine, CCNU and vincristine. Toxicities were minimal as only one patient experienced grade 3 leukopenia. The two patients that received labradimil at 300 ng/kg and carboplatin at 600 mg only experienced grade 1-2 nausea and vomiting. The most common toxicity was grade 1-2 headache which occurred in five of twelve patients. One of the GBM patients had a best response of stable disease, although two patients with anaplastic astrocytomas had partial responses and the time to progression in the three anaplastic astrocytoma patients was 60, 64 and 106 weeks. This study demonstrated that intra-carotid labradimil at 300 ng/kg plus carboplatin could produce responses in patients with malignant glioma and that the responses may be durable. In addition to this small phase I study, a phase II trial in Western Europe evaluated the efficacy of intravenous labradimil (300 ng/kg) with carboplatin in 87 patients with recurrent malignant gliomas (28). In patients that had no prior chemotherapy the combination of labradimil and carboplatin either stabilized or lead to objective responses in 79% of the patients. These studies suggest that labradimil in combination with an agent that has limited efficacy in the treatment of glioma (carboplatin) could be combined to produce radiographic responses in malignant gliomas. A phase I/II study compared intra-venous labradimil (300 ng/kg) and carboplatin versus a placebo and carboplatin in patients that

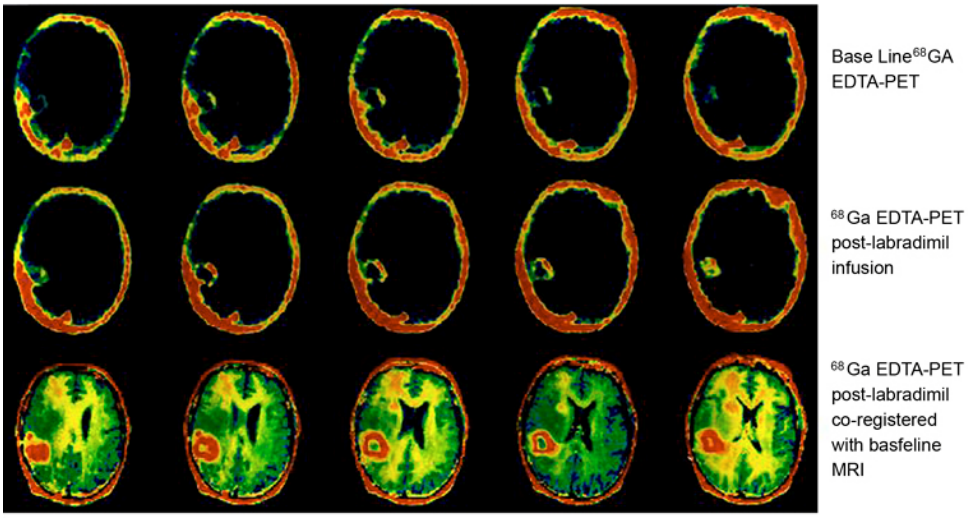

Figure 1. 68Ga EDTA Axial Brain PET obtained in patients with malignant gliomas. Upper Row: Baseline axial PET images. Center Row: Axial PET images obtained after infusion of 100 ng/kg labradimil. Lower Row: Axial T 1 -weighted MR images showing co-registration of baseline MRI and labradimil PET images. The images were scaled separately for each image set with the maximum value of the image set on the top color of the scale (30). Reproduced with permission from Rockwater Inc.

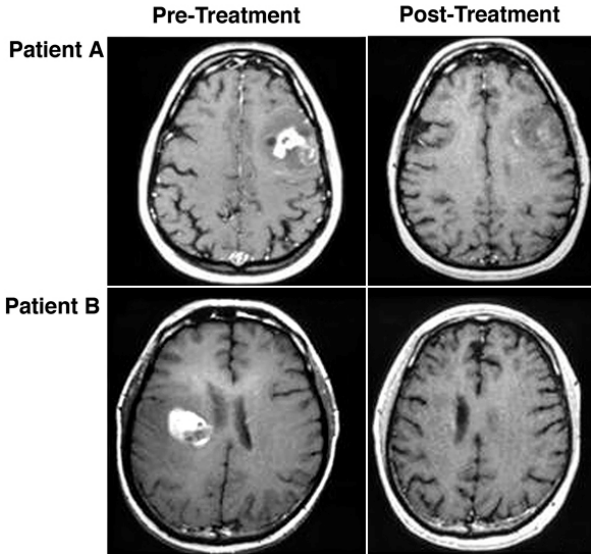

Figure 2. Radiographic responses of patients with malignant glioma treated with labradimil and carboplatin. Axial T 1 -weighted MR images obtained in two of the three patients showing at least a 50% reduction in tumor volume after treatment with 300 ng/kg labradimil and carboplatin. Upper Left and Right: Patient A. Pre-study and response scans, respectively. Lower Left and Right: Patient B. Pre-study and response scans, respectively (30). Reproduced with permission from Rockwater Inc.

were chemo-naive or previously treated patients with recurrent malignant glioma (29). Carboplatin was dose based on the Calvert method to an AUC of 7. Sixty-one patients received labradimil plus carboplatin while 60 patients received a placebo plus carboplatin. This study failed to show a statistically significant difference in radiographic responses or median time to progression between the groups. The authors of the study suggested that the lack of efficacy of labradimil was caused by the intravenous dose of labradimil being too low to improve delivery of carboplatin across the BTB.

There are several important issues regarding the ability of labradimil to increase the delivery of chemotherapy to CNS tumors. Although clinical trials have attempted to document the maximum tolerated dose (MTD) and efficacy associated with the use of labradimil a large percentage of these studies were unable to document a formal MTD and as a result subsequent phase II studies lead to conflicting results (28, 29). There has been a dose escalation study performed that has formally documented an MTD as being nearly five times the dose of intravenous labradimil previously evaluated. Emerich (2001) reported a

phase I/II study carried out in Western-Europe that attempted to determine the MTD and efficacy of labradimil in combination with carboplatin in patients with CNS metastatic non-small cell and small cell lung carcinoma (31). Dose levels of labradimil were initiated at 300 ng/kg and increased in 150 ng/kg increments up to 1800 ng/kg. Carboplatin was dosed to an AUC =7 and cycles were repeated every four weeks. There was no increase in hematologic toxicity seen at any labradimil dose level. Previously unseen toxicities were observed such as urinary urgency and subtle alterations in sensorium. Previously reported toxicities were described at a greater frequency at the highest dose levels such as abdominal pain, headache, xerostomia, diarrhea, dyspepsia. There was a dose response relationship for patients with brain metastases from NSCLC. For patients that received labradimil < 1200 ng/kg the objective radiographic response rate was approximately 15%. In contrast, patients that received labradimil >1200ng/kg the response rate was nearly 50%. The MTD of labradimil was determine to be close to 1500ng/kg administered with carboplatin (AUC=7) every 4 weeks. This study has lead to several important conclusions: 1) if labradimil is administered intravenously, it must be given in high enough doses to optimally stimulate B2 receptors in brain tumors and 2) the toxicity associated with high dose (>1200 ng/kg), intravenous labradimil in combination with carboplatin is well tolerated.

The mechanism of action of labradimil has been ascribed to its ability to increase the vesicular transport of chemotherapy across the BTB by activation of B2 receptors. There is growing evidence that increases in intra-tumoral pressure may impede the trans-capillary flow of chemotherapy from the intravascular space to the interstitial space of solid tumors either within the CNS or at the extra-cranial sites (32, 33). Labradimil can decrease interstitial tumor pressure and increase the intra-tumoral concentration of chemotherapy in tumors located at intra-cranial and at extra-cranial sites (34, 35). As a result, there is an additional rational for combining high dose labradimil with chemotherapeutic agents known to be effective in the treatment of systemic neoplasms and neoplasms within the CNS.

4.INTRA-CAVITARY/INTRA-TUMORAL DELIVERY OF THERAPEUTIC AGENTS FOR THE TREATMENT OF CNS NEOPLASMS

The direct intra-cavitary delivery of therapeutic agents such as chemotherapy laden wafers, micro-infusion of immunotoxins or monoclonal antibodies are attractive methods of circumventing the BTB. Direct intra-cavitary delivery of a therapeutic agent produces high concentrations of agent directly in the tumor bed potentially improving local control of disease. Since a majority of malignant glioma recurrences occur within a short distance from the initial tumor (36) local control maybe of importance. Systemically delivered agents are limited in their ability to penetrate the BTB and accumulated with in neoplasms in the CNS (37). This makes the delivery of an agent directly into the resection cavity an attractive method of delivery. In addition, intra-cavitary delivered therapy largely circumvents the systemic toxicity associated with systemically delivered chemotherapy.

4.1.Compartmental delivered chemotherapy impregnated wafers

Nitrosoureas are among the most widely used agents in the treatment of CNS neoplasms. This largely stems from the high lipophilicity of these agents and hence their ability to penetrate the BBB. These agents have had only modest activity in clinical studies and there is toxicity associated with the systemic administration of this class of agents. In an effort to increase the local concentration and at the same time minimize the dose limiting systemic toxicities associated with nitrosoureas, a nitrosourea impregnated dissolvable polymer has been developed. A dissolvable polyanhydride matrix (poly [1, 3-bis (carboxyphenoxy) propane-co-sabecic-acid) impregnated with BCNU 3.8% (7.7mg/wafer) has been evaluated in patients with recurrent and newly diagnosed glioblastoma multiforme. Animal studies have demonstrated that almost 100% of the BCNU is released within 120 hours although most of the agent (75%) is released within the first within 60 hours after wafer implantation. The initial clinical study evaluating the safety and toxicity of chemotherapy impregnated biodegradable polymer was conducted in 21 patients with recurrent malignant gliomas (60% diagnosed with glioblastoma multiforme). Patients were treated at one of three dose levels of BCNU-impregnated wafer (Group 1 1.93% [3.85 mg/wafer], Group 2 3.85% (7.7 mg/wafer], or Group 3, 6.35% [12.7 mg/wafer]) (38). Patients had maximum tumor resection and most patients received 8 wafers. Approximately half of the patient population received prior chemotherapy and one patient was previously treated with ^{125}I implants. The mean post implant survival times for group 1, 2 and 3 were 65, 64 and 32 weeks, respectively. The median survival times for groups 1, 2 and 3 were 65, 47 and 23 weeks, respectively. Seizures were described in patients with a previous history of seizures and patients did require a prolonged taper of dexamethasone for the management of symptomatic vasogenic edema. Based on the lack of systemic toxicity and manageable local toxicity a randomized, placebo-controlled clinical trial was performed (6). This multi-institutional study in the United States and Canada enrolled 222 patients from 27 medical centers. Patient with recurrent malignant glioma were enrolled. Patients underwent maximum resection and were randomized to either receive 3.85% BCNU-wafer or placebo wafer. Patients were divided based upon the histologic characteristics that suggested “active” or “quiescent” disease. Patients with glioblastoma multiforme that received BCNU-wafers had a statistically significant increase in 6 month survival as compared with those patients that received placebo-wafer (44% vs 64% p=0.02). As in previous studies, systemic and CNS toxicities were well tolerated.

BCNU-copolymer wafers have also been evaluated in patients with newly diagnosed malignant gliomas in a small randomized study, and randomized double-blind study, and a multi-institutional phase III study (39, 6, 40). These studies collectively represent over 300 patients treated with BCNU-copolymer wafer for patients with malignant glioma. Westphal (2003) enrolled 240 patients with newly diagnosed malignant glioma. Patients were similar for factors known to alter prognosis. Patients were randomized to either receive placebo wafers or BCNU-

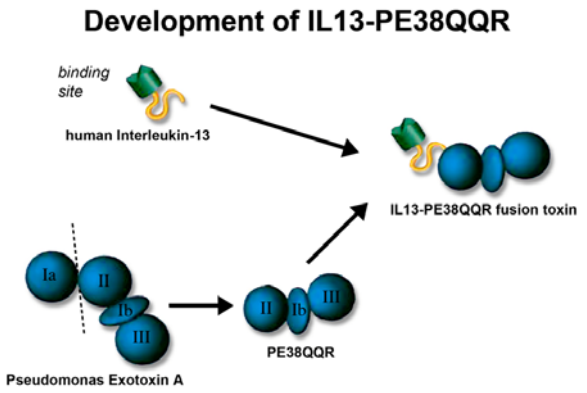

Figure 3. The structure of IL-13PEQQRR. IL-13PEQQRR is a fusion protein consisting of IL-13 and Pseudomonas Exotoxin A. The Pseudomonas Exotoxin is composed of four subunits, Ia, II Ib and III. Subunit Ia is replaced with an hIL-13 molecule. Subunit III binds to and inhibits elongation factor-2 (EF-2). Inactivation of EF-2 results in cell death. Reproduced with permission from Neopharm Inc..

copolymer wafers at the time of initial tumor resection (40). Patients subsequently received standard external beam. For patients that received BCNU-copolymer wafer there was and increase in median survival from 13.9 months as compared to those patients that received placebo wafer, 11.6 months ($p=0.03$). For patients that received BCNU-copolymer there was a 29% reduction in risk of death, and clinical decline was statistically significantly longer ($p \leq 0.05$). CSF leak and intracranial hypertension was more common in those patients that received BCNU-copolymer wafer. No significant systemic toxicities were observed and CNS toxicities were averted with optimal surgical and medical management. Collectively, these findings suggest that BCNU-copolymer used at initial tumor resection or at first tumor recurrence may improve outcomes for patients with malignant glioma.

BCNU-copolymers are currently being evaluated for the treatment of metastatic CNS disease. In addition, there are also ongoing clinical trials that combine BCNU-copolymer wafer with O6-benzylguanine (O6-BG). O6-BG inhibits AGT (alkyl-guanine alkyl transferase -AGT). AGT repairs the O6 methylation of guanine produced by nitrosoureas and is expressed in several human solid tumors including malignant glioma. There are several agents that have activity against malignant CNS tumors that are being evaluated in pre-clincal studies via delivery by direct intra-cerebral wafers including taxanes (paclitaxel, docetaxel), cyclophosphmide, adriamycin, and irinotecan.

4.2. Convection Enhanced Delivery (CED) of Immunotoxins

The use of compartmentally delivered therapy such as wafers is a novel method of delivering chemotherapy directly into the surgically created resection cavity. Although the use of chemotherapy impregnated wafers allows a relatively high concentration of chemotherapy to be delivered directly to the tumor bed without significant systemic toxicity there are important limitations of BCNU impregnated wafers. The ability of the chemotherapy to distribute throughout the cavity is dependant upon diffusion, the passive dispersion of the chemotherapeutic agent. As a result, the distribution of the chemotherapeutic agent is dependant upon the interstitial pressure adjacent to the resection cavity and the molecular weight of the agent. In animal models using wafers that contain > 3x the dose used in humans, [H^3]-BCNU was detected only 1-1.2 cm diameter around the wafer 72 hours after implantation (41). Considering that 90% of malignant gliomas recur within a 2 cm margin of the initial resection cavity BCNU laden wafers may deliver agent to a limited area.

In an attempt to improve the distribution of chemotherapy directly into tumor tissue or adjacent tissue pre-clinical studies have defined the technique of delivering agents under positive pressure (convection) (42, 43). Not only does CED of therapeutic agents obviate the systemic toxicities associated with the systemic delivery of chemotherapy but in addition high molecular weight agents can be dispersed in a relatively homogenous manner into areas of residual tumor and along white matter tracts where tumor cells tend to disseminate. This allows for a significant increase in the volume of distribution of the agent locally in contrast to chemotherapy laden wafers which penetrates the tumor cavity surface by only several millimeters.

Conjugated-immunotoxins via CED are the agents that have been the most extensively evaluated in clinical trials for the treatment of surpratentorial primary brain tumors. Convection enhanced delivery of a chimeric anti-bodies targeting histones (Cotara®) has been evaluated for the treatment of malignant gliomas (44). Pre-clinical studies have evaluated the delivery of liposomes, chemotherapy, viral vectors, pro-apoptotic agents by CED (45-48). Furthermore, animal studies have evaluated the feasibility of CED into lesions that reside within the brain stem (49). Recently, CED of viral vectors and paclitaxel has been evaluated in clinical trials with promising results (50,51) though conjugated immunotoxins remain the most extensively studied agent delivered by CED in humans. Several clinical trials have assessed the toxicity and efficacy of the CED of conjugated immunotoxins that target one of several receptors including epidermal growth factor receptor (7), human transferin receptor (52), IL-4 receptor (8) and more recently IL-13Rα2 (53). The cytotoxic portion of all of these immunotoxins is derived from either, diphtheria toxin or pseudomonas exotoxin (PE). Most of the current clinical trials have employed conjugated immunotoxins incorporating PE though both toxins inhibit protein synthesis by similar mechanisms. The pseudomonas exotoxin is a 66-kDa protein composed of four subunits (Ia, Ib, II, and III) (see Figure 3). The Ia subunit of the PE is substituted by one of several molecules that bind to relevant receptors expressed in malignant CNS neoplasms. After internalization by the targeted receptor system, subunit III, the cyto-toxic portion of the molecule, inhibits ADP-ribosylation of elongation factor-2 (EF-2) and protein synthesis (see Figure 4) leading to cell death. This is an extremely potent cytotoxic agent as only one molecule of the conjugated immunotoxin is needed for the death of a single tumor cell.

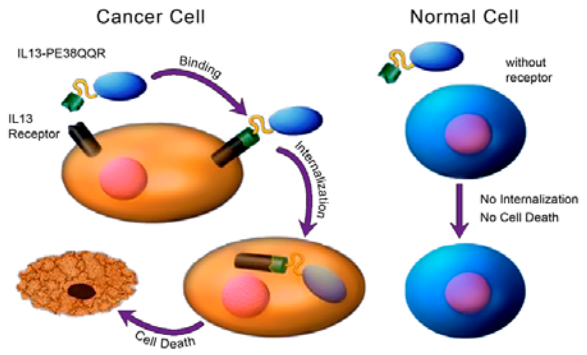

Figure 4. IL-13PEQQRR binds tumor cells that express IL-13α2r. The receptor is highly expressed on malignant gliomas and is not expressed on normal CNS tissue. After binding and internalization of IL-13PEQQRR subunit III binds EF-2 inhibits ADP-dependant ribosylation and leads to cell death. Reproduced with permission from Neopharm Inc..

EGFR, human transferin receptor, interlukin-4 receptor and interlukin-13 receptor have been localized to CNS tumor tissue. To date there have been over 200 patients that have been treated with convection enhanced delivery of immuno-toxins and the associated toxicity and efficacy has been evaluated (see Table 4). The most common toxicities describe include headache, seizure, weakness. All of these toxicities were reversible though if not reversible were thought to be attributable to tumor progression (54, 7, 55). Symptomatic brain necrosis was seen in patients that received "high" concentrations of immunotoxin though only a single group observed that a substantial number of their patients required surgical intervention for medical refractory cerebral edema (8). In phase I and phase II studies of immunotoxins delivered by CED response rates have varied from 60% to 15%. Sampson (2003) describe a response rate of 15% in their patients though the maximum tolerated dose of TP-38 was not determined. The infusion of an immunotoxin targeting the tumor or residual tumor is not necessarily thought of as an immediate process. There have been several groups that have described interval "disease progression" as documented by increase in enhancement on cranial MRI adjacent the resection cavity and at distant sites though within the area of distribution of drug delivery. Subsequent interval imaging revealed a near complete response without added surgical or medical intervention (7, 53). These findings may suggest that there may be a "late" immunologic response associated the delivery of an immuno-toxin by CED.

Convection enhanced delivery of potent immuno-toxins is a safe and potentially an effective method of the treatment of CNS neoplasms. The 3-dimensional space within which a malignant CNS neoplasm resides is not a uniform sphere. In addition vasogenic edema and resultant intratumoral pressures can be very heterogeneous. Most of the vasogenic edema disperses along white matter tracts though anatomy and resultant patterns of pressures and fluid distribution change. Optimal catheter placement has been associated with improved survival (53). In an effort to optimize and reduce the variability of the distribution of immunotoxins delivered by convection enhanced delivery in clinical trials MRI and PET techniques have been used to evaluate and optimize drug delivery. Weber 2003 (56) described the use MRI sequences (diffusion tensor imaging [DTI] and diffusion weighted imaging [DWI]) to assess the distribution of gadolinium (Gd) and paclitaxel in five patients. Diffusion tensor MRI sequences were obtained to assess the directional flow of interstitial fluid prior to direct intra-cerebral micro-infusion of Gd. DTI data was entered into a computer algorithm that predicted the distribution of Gd based on fluid dynamics of the brain tissue. Patients under went a 48 hour infusion of Gd/saline and a second infusion of paclitaxel for 96 hours. To observe actual distribution of Gd delivered by CED T1-weighted MRIs were obtained at 12, 24 and 48 hours after the start of the initial infusion. DWI was obtained to visualized the effect on brain tissue related to paclitaxel. To assess the predictive accuracy of DTI –generated data and T1-Gd images post infusion were compared. DTI-generated data was also compared with DWI to assess the predictive accuracy of the co-infused agent. The DTI- data accurately predicted T1-Gd distribution and DWI changes were in concordance with distribution of enhancement. Nuclear medicine imaging techniques have also been used to evaluate the distribution convection enhanced delivery of an immunotoxin (57). Computer generated algorithms that assist the neurosurgeon optimal catheter placement will add validity to the evaluation of CED using various immunotoxins in ongoing phase III multi-institutional trials.

4.3. Monoclonal antibodies

The identification of biologically relevant epitopes associated with neoplasms and the technology to develop highly specific anti-bodies have resulted in new methods for the treatment of human malignancies. antibodies are currently being evaluated in clinical trials for the treatment of a host of neoplasms including malignant gliomas. For example, the efficacy of monoclonal antibodies targeting epidermal growth factor receptor and vascular endothelial growth factor has been evaluated in selected patients with metastatic breast carcinoma and colorectal carcinoma, respectively (58,59). Monoclonal antibodies can target specific receptors or can be conjugated with radioactive-isotopes as a method of delivering localized brachytherapy. Monoclonal anti-bodies for the treatment of extra-cranial neoplasms can be delivered systemically though the BBB/BTB limits large molecular weight agents, including monoclonal anti-bodies from entry into the CNS (37). The delivery of monoclonal antibodies for the treatment of CNS neoplasms requires administration via intra-thecal, intra-cavitary or intra-tumoral routes.

Several groups have evaluated the toxicity and efficacy of monoclonal antibodies armed with a radioactive isotopes for the intra-cavitary, intra-tumor or intra-thecal treatement of malignant gliomas and leptomeningeal disease (9, 60-66). Antibodies directed at tenasin-c (81C6/BC2/BC4) and neural cell adhesion molecule (ERIC-1) have been armed with beta-emitters such as Y-90 or I^{131}.

Table 4. Clinical Trials Evaluating the efficacy and toxicity of Immunotoxins and other agents delivered by direct intra-cerebral micro-infusion for the treatment of CNS tumors

Phase	Histology	Immunotoxin	N	Response Rate	Toxicity (≥ grade 3)	References
I	GBM/adenocarcinoma	TF-CRM107	18	60%	NR	51
II	Recurrent Malignant Glioma	TF-CRM107	44	35%	Fatal cerebral edema[1]	50
I	Recurrent GBM [2]	TP-38	15	15%	Fatigue, Weakness[3], Headache [4]	7[5]
I	Malignant Glioma	IL-13PE38QQRR	24	NR	None	52
I/II	Recurrent Malignant Glioma	IL-13PE38QQRR	18	11%	Cerebral edema	53[6]
I	Recurrent GBM	IL-4PE38KDEL	9	NR	Cerebral edema	8
I	Recurent GBM	HSV-Tk	8	75%	None	49
I/II	Recurrent Malignant Glioma	Paclitaxel	15	73%	Wound dehiscence, Wound infection, Transient chemical meningitis, Transient neurological decline	51
III	1st Recurrent GBM	IL-13PE38QQR	Currently accruing			Neopharm (Precise)
III	Recurrent, unresectable GBM	TF-CRM107	Currently accruing			Xenova
III	Newly diagnosed GBM prior to radiation therapy with or without temozolomide	IL-13PE38QQR	Currently accruing			Neopharm [7]

[1] Fatal cerebral edema. Family decided against further medical or surgical management, [2] Maximum tolerated dose not reached, [3] Related to tumor progression, [4] Reversible, [5] 80% of patient were GBM with the remaining being 1 gliosarcoma, 1 anaplastic astrocytoma, 1 anaplastic oligodendroglioma and 1 metastatic sarcoma, [6] Seven patients with GBM, 8 patients with "high grade glioma", 3 patients with anaplastic astrocytoma, [7] Non-randomized, open label, dose comparison, single group assignment, safety study. Following treatment with CED-IL-13PEQQRR, all patients will receive standard course of radiation therapy. Some patients will receive Temozolomide with radiation therapy followed by adjuvant Temozolomide, NR-Not reported

The most extensively studied monoclonal antibody is I^{131}-81C6 which is an IgG_{2b} anti-body that avidly binds the hexabrachian, extracellular matrix protein, tenasin-c (See Figure 5). This protein/epitope is not expressed in normal brain tissue though is highly expressed in glioblastoma multiforme as well as other solid tumors including melanoma, breast, lung and squamous cell carcinoma (See Figure 6).

The local and systemic toxicity associated with the intracranial administration of monoclonal antibodies has been described (63, 65). A phase I dose escalation study assessed the toxicity associated with ^{131}I 81C6 in patients recurrent malignant gliomas (63). In this study thirty four patients were enrolled, twenty-six of which had recurrent glioblastoma multiforme, three with recurrent anaplastic astrocytoma, two with recurrent oligodendroglioma, two with recurrent malignant melanoma and one patient had recurrent ependymoma. All patients had gross total resections performed with the maximum residual tumor of a 1 cm margin. At the time of surgery patients had either a Rickham or an Ommya reservoir placed. The reservoir was then assessed for optimal placement. Patients had ^{99m}Tc-labeled albumin injected into the cavity through the reservoir and a gamma camera was used to detect radioactivity associated with the area adjacent the reservoir and adjacent cortex at times 0, 4 and 24 hours after injection (See Figure 7). If distribution of radio-pharmaceutical was limited to the resection cavity (i.e. no radioactivity with in subarachnoid space, or along reservoir track) patients received treatment with ^{131}I 81C6 through the reservoir. Patients were initially treated at 20 miC of ^{131}I and were dose escalated in cohorts of three patients. Dose escalation proceeded in 20miC increments. A total of twenty patients received 80 mCi or lower and there was no toxicity observed in any of these patients. For those patients that received > 80mCi eight patients experienced grade III or grade IV hematologic toxicity. No patients experienced serious sequela as a result of hematologic toxicity. At doses > 80 mCi, two patients experienced controllable seizures. Three of the five patients that received > 80 mCi had serious neurologic toxicity consisting of progressive hemiparesis, aphasia, and headache. Four of the five patients that received 120 mCi had dose limiting toxicities though none of the eleven patients treated at the 100 mCi experienced any dose limiting toxicity therefore for previously irradiated patients the MTD was defined at 100 mCi. Since all patients had gross total resections survival data was assessed. The median survival of all patients was 60 weeks (95% CI, 42.7-∞) and the probability of 1 year survival was 0.59 (95% CI, 0.44-0.78). For patients with GBMs the median survival was 56 weeks (95% CI, 35.3- ∞). This phase I study showed that an "armed" monoclonal antibody targeting a tumor associated epitope could be delivered with acceptable toxicity and survival data was encouraging. A similar phase I study using intracavitary ^{131}I 81C6 was performed in patients with newly diagnosed malignant glioma with same method has described been described. For patients that had not received previous radiation or chemotherapy the MTD was defined as 120 mCi.

Additional phase II studies for patients with newly diagnosed and recurrent malignant glioma have been completed (9, 66). For all patients treatement with ^{131}I 81C6 produced a median survival of 86.7 weeks and for patients the newly diagnosed glioblastoma multiforme the median survival was 79.4 weeks (9). The phase II study of ^{131}I 81C6 for patients with recurrent malignant glioma was also performed. The median age was 54.5 years and 27 patients (64%) were males. All patients received 100mCi except for two patients that received 67mCi and 75mCi respectively due to the limited size of the SCRC. Toxicities were divided into acute (< 4 weeks), sub-acute (4-16 weeks) and delayed (>16 weeks) periods. Acute and sub-acute reversible, grade 4 hematologic toxicity was seen in 2 patients (4%) and 3 (7%) patients, respectively. Delayed

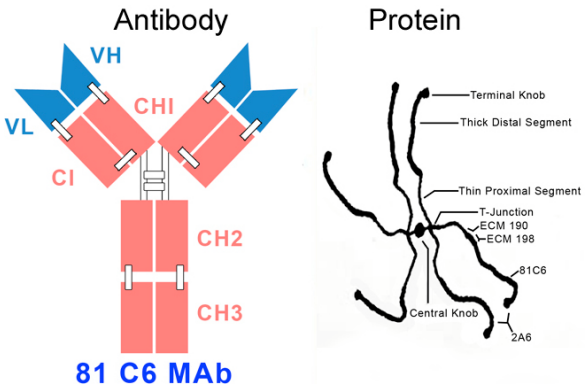

Figure 5. 81C6 anti-tenascin monoclonal anti-body and the structure of tenascin. 81C6 a murine IgG2b armed with I^{131} and delivered into a surgically created resection cavity via an intra-cavitary reservoir. 81C6 binds the thick distal segment of the hexa-brachian extra-cellular matrix protein, tenascin, found in malignant glioma tissue. Reproduced with permission (9).

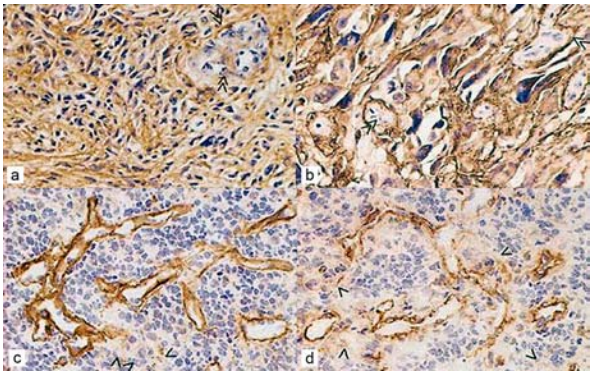

Figure 6. The expression of tenascin in malignant gliomas. Malignant gliomas express substantial levels of tenacin which is seen throughout specimen (panel a and b) while there is minimal localization of tenacin in normal brain tissue though there is localization of tenacin to the normal vascular endothelium. Reproduced with permission (Bigner DD unpublished data).

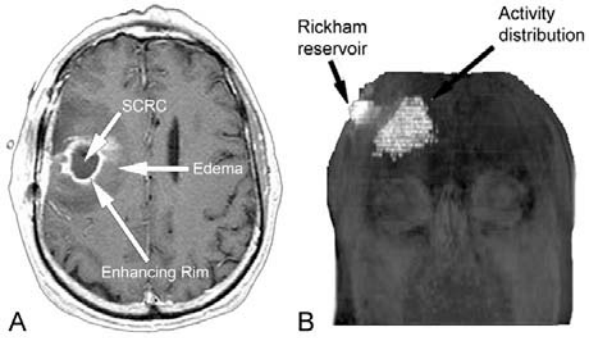

Figure 7. Localization and distribution of 81C6- I^{131}. Axial T1-post Gd sequence with surgically created resection cavity (panel a). SPECT imaging study depicting the distribution of 81C6- ^{131}I delivered into a surgically created resection cavity through a Rickham reservoir. Reproduced with permission (9).

grade 3 or 4 neurotoxicity was seen in 2 patients (4%). The median survival of all patients and GBM patients was 59 weeks for both groups, respectively. For patients with GBM the probability of 1-year survival is 0.56 (CI-95%; 0.41-0.78) (66). I^{131}- labeled murine anti-tenascin antibody 81C6 is associated with minimal hematologic toxicity and provides an improvement in survival in patients with newly diagnosed or recurrent malignant glioma that have failed conventional therapy. Currently, there are additional studies evaluating methods to improve penetration and distribution of monoclonal antibodies using agents that alter the permeability of the BTB as well as other studies evaluating arming this antibody with other isotopes intended to improve the penetration of radioactivity. Additional phase III studies will help to further define the role of intra-cavitary delivered monoclonal antibodies for patients with recurrent malignant glioma.

5. FUTURE DIRECTIONS

5.1. Bone-marrow derived stems cells as delivery vehicles for the treatment of CNS neoplasms

All of the current methods of delivery and agents that are being evaluated in humans for the treatment of malignant brain tumors represent either systemic administration of chemotherapy augmented by agents that are meant to improve the delivery of the agent(s) or the delivery of a therapeutic agent directly into or adjacent the resection cavity. All of these approaches represent methods of attempting to control microscopic or gross residual disease. The morbidity and mortality for patients with malignant gliomas largely arise from the microscopic foci that remains uncontrolled with chemotherapy and which subsequently progressively grows. In an attempt to target the microscopic foci of malignant cells various group have shown that bone-marrow derived stem cells exhibit a prominent amount of tropism for malignant neoplastic cells, and brain tissue injury (67, 68). Transfection of tumor necrosis factor apoptosis inducing ligand (TRAIL) into bone-marrow derived stem cells (BMDSC) exhibits tropisms for malignant tissue implanted into animals and initiates apoptosis in those implanted tumors (69). BMDSC may be used for the delivery of chemotherapy and/or vectors for the treatment of CNS neoplasms. The use of BMDSC as delivery vehicles for the treatment of malignant gliomas remains confined to the basic science laboratory though several groups are committed to translating this technology into clinical trials for patient with CNS neoplasms.

6. CONCLUSION

The treatment of primary and metastatic CNS neoplasms has largely consisted of surgical resection followed by radiation therapy. More recently the use of chemotherapeutic agents for the treatment of CNS neoplasms has resulted in further modest increases in survival for these patients (70). CNS neoplasms remain difficult to treat for several different reasons including the expression of DNA repair enzymes, multi-drug resistance pumps, the derangement of multiple intracellular pathways involved with apoptosis, invasion, and angiogenesis.

Although chemotherapeutic agents can cause various DNA lesions leading to apoptosis and many new

small molecules inhibitors antagonize a particular intracellular system, the systemic administration of any chemotherapeutic or biologic agent results in minute concentrations reaching the CNS neoplasm. This is largely the result of the BTB limiting the penetration of these agents entry into the CNS. BTB permeability is increased in a very heterogeneous manner though a majority of the tumor volume remains impermeable to many chemotherapeutic agents. This ultimately leaves a large volume of tumor untreated and leaves microscopic foci of neoplastic cells untreated.

Since the BTB remains an extremely important anatomic structure that limits the accumulation of chemotherapeutic agents in the CNS tumor many groups have attempted to circumvent the BTB by intra-arterial administration of chemotherapy with or without hyperosmotic blood brain barrier disruption. The molecular and cellular biology of the BTB continues to be elucidated and we have been able to pharmacologically increase the BTB permeability by vaso-active substances. Other groups have decided to increase the concentration of therapeutic agents directly into the surgically created resection cavity by delivering chemotherapy laden wafers, monoclonal antibodies armed with radioactive isotopes and more recently the direct micro-infusion of agents into the tumor or tissue adjacent the tumor bed. Several of these methods circumventing the BTB have resulted in improved outcomes and other methods have yet to be clearly defined. It is clear that for the successful treatment of CNS neoplasms circumventing the BTB and increasing the local concentration of therapeutic agents at the site of the CNS tumor is of paramount importance.

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