Inhibition of the blood brain barrier In Treatment of Recurrent Malignant Primary brain tumors

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A. Study Purpose and Rationale

It is estimated that 17,000 new cases of malignant primary brain tumors were diagnosed in the United States in 2002 (1). Glioblastoma multiforme and anaplastic astrocytoma, which constitute the majority of these tumors, are malignant tumors that are incurable, even with aggressive surgery, radiotherapy, and chemotherapy. The treatment of malignant primary brain tumors in most cases begins with surgical resection of as much tumor as can be performed safely. Radical resection is usually not feasible because of damage to adjacent vital normal tissue. Following surgery, external radiotherapy is used to shrink residual tumor. Radiation is one of the most important modalities for controlling malignant brain tumors, but is not curative. With very rare exceptions, all malignant aggressive brain tumors recur despite surgery and radiotherapy.

Chemotherapy is used as adjuvant therapy for primary brain tumors and to reduce or delay tumor recurrence. The treatment and progress against primary tumors in the CNS has been hampered by at least two major forms of drug resistance: intrinsic resistance in tumor cells similar to extra-CNS malignancies and the blood brain barrier (BBB). The latter form, BBB, is an important mechanism by which the CNS protects itself against various xenotoxins that humans are exposed to on a daily basis. The number of chemotherapy agents that easily cross the intact BBB, are limited to the lipophilic alkylators (BCNU, CCNU, thio-tepa, temozolamide) and high doses of certain antimetabolites (ara-C, methotrexate) for the most part (2). Many of the non-lipophilic alkylators and natural product agents that target topoisomerase I, II and microtubules do not cross the intact BBB at more that 10-20% of their serum concentration (2). Thus, it is vital to the progress of chemotherapy treatments for CNS cancers to functionally inhibit the BBB, in and around a tumor.

Prior studies in primary brain tumors have suggested that the BBB is partially or fully abrogated in the central necrotic tumor bed. In contrast, studies have found that the BBB is partially or fully intact at the peripheral edge of brain tumors and the normal surrounding brain, respectively (3). In primary brain tumors, recurrence usually occurs within 1-2 cm of the surgical margin so that the deposition of drug into the periphery of the tumor and at the normal brain tumor edge interface is an important factor and it has not been fully addressed by previous studies. Thus, the goal of this proposal is to increase the penetration of chemotherapy agents into the growing edges and normal surrounding brain tissue where relapses occur. This could be an important step forward in the treatment of these tumors because a large number of heretofore "inactive" drugs do not enter the CNS and are derived from natural product toxins and do not cross the BBB well. These may become useful for treating gliomas if they can traverse the BBB in significant concentrations.

The BBB and blood-tumor barrier (BTB) are composed of tightly interdigitated capillary endothelial cells that prevent the passage of large, charged molecules including the majority of natural product anticancer agents such as paclitaxel. Though paclitaxel was extremely effective in vitro against glioma cells for inducing apoptosis, it was ineffective in clinical trials in patients with gliomas, a study done jointly at Columbia with NABTT (4). The major protein constituent of the BBB-BTB has been shown to be P-glycoprotein (Pgp). Pgp is also responsible for the multidrug resistant phenotype (MDR) in cancer cells. This membrane protein, ATP-dependent pump binds many structurally unrelated chemotherapy drug toxins that are derived from nature, such as paclitaxel, and effluxes the drugs out of the BBB and BTB into the serum. Since the BBB barrier normally protects our brain from natural xenobiotics it is understandable why they would also prevent the penetration of natural product chemotherapy drug toxins that are derived from natural sources such as fungi, trees and plants. These

natural product toxins comprise over 50% of our current chemotherapy drugs. Thus, over half of all the cancer chemotherapy drugs that are useful in the treatment of non-brain cancers are not helpful in the treatment of gliomas because of the BBB and BTB. Though intrinsic drug resistance to these natural agents may also induce resistance once the drug enters glioma cells, it is important to first circumvent the resistance caused by this barrier (BBB-BTB) which may then allow us to investigate the clinical usefulness of these agents.

There are many effective inhibitors of Pgp available for investigation in brain, as well as, non-brain tumors. However, in relation to gliomas, there are four reasons why these natural product anticancer agents have not been useful to date: 1) The BBB-BTB barrier as discussed above; 2) Toxicity – many potent inhibitors of Pgp, such as calcium channel blockers and cyclosporine and its derivatives, have toxic effects at the concentration needed to inhibit the Pgp pump; 3) Pharmacokinetic changes – since Pgp also exists and functions in organs for detoxification such as the kidney, liver, intestines which are important in the elimination of various anti cancer drugs, inhibition of Pgp led to unexpected increases in serum concentrations of the anti-cancer drug. Therefore, many studies were done with half the dosage of the anti-cancer drug because the kidney or liver Pgp was also inhibited – leading to a doubling of serum concentrations of anticancer natural product agents; 4) Multiple mechanisms of drug resistance -- cancer cells, especially those with mutant p53, have multiple mechanisms of drug resistance operative at the same time in a single tumor cell so that even if Pgp is inhibited one may not achieve reversal of drug resistance and apoptosis. However, the advantage of this proposal is that the cells of the BBB-BTB are not malignant but normal capillary endothelial cells that do not have multiple mechanisms of resistance and we postulate that, once Pgp is inhibited, the drugs should get across this barrier. Thus, we chose to study tamoxifen because it is less toxic, its mechanisms of actions are familiar, and it will not alter the pharmacokinetics of paclitaxel.

Tamoxifen is a potent inhibitor of Pgp; in vitro studies showed it can bind to Pgp at drug efflux sites, activate intrinsic Pgp-ATPase pump function leading to tamoxifen efflux in place of chemotherapy efflux, and inhibit activation of PKC-alpha resulting in down-regulation of basal and stimulated pump function. (5). An ongoing randomized clinical trial at CPMC is assessing penetration of paclitaxel – with or without tamoxifen – into brain tumors by measuring tissue levels of paclitaxel following surgical removal of the tumor. Interim analysis of the data found over a 5-fold increase in the paclitaxel deposition in the periphery of the tumor occurred in the paclitaxel/tamoxifen group compared to the paclitaxel alone group. Additionally, pre-treatment with tamoxifen increased paclitaxel deposition into the normal surrounding brain by 4.3-fold. These are important areas because this is where the great majority of relapses occur. These data support the premise that inhibiting Pgp in the BBB enhances deposition of natural product chemotherapy into recurrent brain tumors. A significant implication of our results is that natural product agents traditionally found to be ineffective in brain tumors may prove successful if the BBB is inhibited.

We are currently planning a Phase I study to determine the maximum tolerated dose (MTD) of paclitaxel among patients with brain tumors. The MTD in this specific population is expected to be higher than that seen in other cancer types because these patients are often concurrently prescribed anticonvulsants that stimulate the cytochrome P450 system, and thus ultimately paclitaxel clearance (6). This current proposal will utilize the MTD of paclitaxel in this setting to study the efficacy of chemotherapy regimens that incorporate tamoxifen to "open" the BBB to penetration by another anticancer agent. We will determine if better response rates can be achieved among patients with recurrent primary brain tumors with therapy with paclitaxel/tamoxifen or irinotecan/tamoxifen versus treatment with irinotecan alone. Irinotecan is increasingly used for recurrent malignant gliomas with two recent studies with the same eligibility criteria noting response rates of 9% and 14% respectively (7).

B. Study Design and Statistical Analysis

This study will be a multicenter, prospective, randomized trial to evaluate the efficacy of different chemotherapeutic regimens in the treatment of recurrent primary brain tumors. Oncologist will refer

patients that have a histologically confirmed malignant glioma that was found to have recurred by contrast-enhanced MRI. The patients will be randomized by a block randomization scheme of patient block size 30 at each of the centers to one of the three treatment arms: paclitaxel/tamoxifen, irinotecan/tamoxifen or irinotecan alone. Patients will receive 3-week cycles of chemotherapy unless their tumor progresses or an unacceptable toxicity occurs. Tumor response, the primary outcome, will be assessed by MRI scan every 6 weeks. Tumor response will be classified according to the following criteria: complete response is defined as disappearance of all enhancing tumor; a partial response will be a greater than 50% reduction in tumor volume while the patient is receiving a reduced or stable steroid dose; progressive disease is a greater than 25% increase in tumor volume or the appearance of a new lesion; stable disease is any other response. Patients deemed to have a complete or partial response will have independent determination of their tumor volumes by a single neuroradiologist at CPMC. Patients who demonstrate progression of disease will be discontinued from the study. Toxicities that would require removal of the patient from study include: Grade ¾ cardiac, renal, pulmonary or hepatic toxicities; Grade 4 or irreversible Grade 3 neurotoxicity; more than 2 episodes of febrile neutropenia, and treatment delay of greater than 36 days between chemotherapy infusions. Time to tumor progression and survival – measured from date of registration – will also be measured.

This study is designed based on one key assumption, namely, that the objective response rate with irinotecan alone is 10%. When the data from the two studies detailed in Cloughesy *et al.* (6) are merged– use the same eligibility criteria and starting dose of irinotecan – a combined objective response rate of 10% results. Additionally, a 5% increase in response rate in either of the tamoxifen-containing regimens would be considered of clinical interest. Each arm will therefore enroll 955 subjects, for a study total of 2865 patients. This sample size was calculated for a chi square analysis with a power of 0.80 and an alpha of 0.5 (following Bonferroni correction for three tests). The large study size suggests that accrual will take approximately 6 years with the participation of 20 centers enrolling an average of 25 patients each per year.

C. Study Procedure

Patients that meet eligibility criteria will be randomized to one of the three treatment arms. A medical history, a chest X-ray, a physical examination, a neurological examination and a laboratory evaluation will be obtained. Patients will then be treated according the appropriate scheme illustrated and detailed below. Physical examination, neurological examination and a laboratory evaluation will be repeated at the start of each treatment cycle. MRI will be used to radiologically assess tumor response at 6 and 12 weeks after first dose, and at least every 9 weeks thereafter until disease progression or removal from study secondary to other causes.

a. Tamoxifen-containing arms

After registration, on Day 1, patients will receive a loading dose of tamoxifen at 400 mg/m2 PO as an outpatient and will continue on 150 mg/m2 PO BID for the following 5 days (Days 2-6). Three cycles of 21 cycles each will be administered in total.

b. Paclitaxel/tamoxifen arm

Paclitaxel will be administered intravenously on Day 6, at 330 mg/m^2 IV, over 3 hours. All patients will be premedicated to prevent severe hypersensitivity reactions. The following medications will be used:

- Total dexamethasone 20 mg orally 12 and 6 hours before paclitaxel. This total dose is equal to the baseline dexamethasone that the patients may be taking plus additional dexamethasone given before paclitaxel to equal 20 mg total for each dose.
- Diphenhydramine (or its equivalent) 50 mg IV 30 to 60 minutes prior to paclitaxel.
- Ranitidine (50 mg) IV 30 to 60 minutes prior to paclitaxel.

c. Irinotecan-containing arms

Irinotecan will be administered intravenously on Day 6, at 300 mg/m^2 IV, over 90 minutes. All patients will be premedicated with dexamethasone 10 mg IV as part of an antiemetic regimen.

Paclitaxel/Tamoxifen scheme							
	D_1	D_2	D_3	D_4	D_5	D_6	D_7– D_{21}
TAMOXIFEN 400 mg/m^2 PO	X						No Treatment
TAMOXIFEN 150 mg/m^2 PO BID		X	X	X	X	X	X
PACLITAXEL 330 mg/m^2 IV						X	

Irinotecan/Tamoxifen scheme							
	D_1	D_2	D_3	D_4	D_5	D_6	D_7– D_{21}
TAMOXIFEN 400 mg/m^2 PO	X						No Treatment
TAMOXIFEN 150 mg/m^2 PO BID		X	X	X	X	X	X
IRINOTECAN 300 mg/m^2 IV						X	

Irinotecan scheme							
	D_1	D_2	D_3	D_4	D_5	D_6	D_7– D_{21}
IRINOTECAN 300 mg/m^2 IV						X	No Treatment

D. Study Drugs

The three study drugs are paclitaxel, irinotecan and tamoxifen – which will be administered according to the dosing schedule detailed in the Study Procedure section. None of the three is currently approved by the FDA for the treatment of brain tumors. Potential toxicities stemming from these medications are discussed in the Potential Risks section.

E. Medical Device

N/A

F. Study Questionnaires

N/A

G. Study Subjects

- Patient is >18 years of age.
- Recurrent malignant primary brain tumor, contrast enhanced MRI confirmed.
- Prior therapy allowed including chemotherapy, radiotherapy, stereotactic radiosurgery. A hiatus of 3 weeks and 5 weeks off chemotherapy and radiation, respectively, is necessary.

- No prior therapy with paclitaxel, docetaxel, irinotecan or topotecan allowed.
- Non-pregnant, non-lactating. A negative β-HCG urine or blood test is required before enrollment.
- *Clinical parameters:*

Age	> 18 years.
Performance status	Karnofsky >60%.

- *Required initial laboratory data*:

White cell count	>3000/ul.
Absolute neutrophil count (ANC)	≥1500/ul.
Platelet count	>100,000/ul.
BUN	<1.5 x normal
Creatinine	<1.5 x normal
Total bilirubin	<1.5 x normal
SGOT or SGPT	<2 x normal
Alkaline phosphatase	< 2 x normal

- Informed Consent
- *No serious medical or psychiatric illness* preventing informed consent or intensive treatment e.g., serious infection).
- No recent (prior 6 months) myocardial infarction, angina pectoris, or history of congestive heart failure. Patients with any evidence of a conduction system abnormality (second or third degree heart block, bundle branch block dysrhythmias), or who are taking other medications known to affect the conduction system (*e.g.:* beta blockers, digoxin, other anti-arrhythmics, verapamil) are eligible only if cleared by a cardiologist prior to therapy.
- No concurrent use of oral birth control pills.
- No history of deep venous thrombosis, or pulmonary embolism within the past 6 months, unless an inferior vena caval filter device is in place.
- No history of hypercoaguable state.
- No history of a thrombotic cerebral vascular accident.

H. Recruitment of Subjects

Subjects will be approached and referred by their physician after confirmation of primary brain tumor recurrence following treatment with surgery, radiation, chemotherapy or any combination of these treatment modalities.

I. Confidentiality of Study Data

Study data will be coded and stored in a secure location in accordance with IRB regulations.

J. Potential Conflict of Interest

None.

K. Location of the Study

Multicenter

L. Potential Risks

Patients in this trial are at risk for significant toxicities secondary to the chemotherapy medications. In this case of those on paclitaxel, the most significant toxicities are hematologic – myelosuppression, leukopenia, neutropenia and thrombocytopenia. Recovery in cell counts often occurs within 3 weeks. Severe hypersensitivity reactions may also occur directly following paclitaxel infusion; all patients will receive premedication which significantly reduces the incidence of such reactions. Other potential toxicities include bradycardia, peripheral neuropathy, arthralgia, myalgia, liver function abnormalities, mucositis, stomatitis, and alopecia.

A significant, potentially life-threatening toxicity associated with irinotecan use is diarrhea. Early diarrhea occurs within 24 hours of administration and may be managed with atropine. Late diarrhea occurs later than 24 hours after treatment and is managed with high-dose loperamide if necessary. Other significant toxicities associated with irinotecan include myelosuppression, nausea and vomiting, weakness, vasodilation, dyspnea and insomnia.

Tamoxifen use has been associated with an increased incidence of thromboembolic events, e.g. stroke and pulmonary emboli. Other notable adverse reactions include decreased visual acuity, retinopathy, corneal changes, headaches, dizziness, cerebellar ataxia, fluid retention, nausea and menstrual irregularities.

M. Potential Benefits

If the study treatment in any of the three arms is effective, those patients may have a longer disease-free period than would have been obtained with conventional treatment. In addition, the data gathered through this trial will benefit society by helping to refine treatment decisions for future patients with recurrent primary brain tumors.

N. Alternative Therapies

Other potential approaches to treating these patients include:

1. Treatment with conventional doses of single agent or combination chemotherapy.
2. New experimental chemotherapeutic agents.
3. No therapy, or supportive care without chemotherapy.

O. Compensation to Subjects

None.

P. Cost to Subjects

None. Insurance approval will be actively sought.

Q. Minors as Research Subject

N/A

R. References

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