PBTC-005 Abstract for Health Professionals

Study Title: Phase I Trial of Temozolomide and O^6-Benzylguanine in Pediatric Patients with Recurrent Brain Tumors

Description:

Stratum 1 will accrue relapsed patients who have been treated with focal radiation therapy and patients who have not received radiation therapy. Stratum 2 will accrue patients who have had prior craniospinal irradiation or myeloblative therapy. If neutropenia is the dose limiting toxicity in either strata, as anticipated by the adult phase I study, additional patients will be accrued allowing the use of G-CSF to establish whether higher doses of temozolomide can be administered with this form of hematological support.

Stratification Scheme			
Stratum 1		***Stratum 2***	
No prior RT or prior focal RT only		Prior craniospinal radiation (³18 Gy) or myeloablative therapy	
Stratum 1a	***Stratum 1b****	***Stratum 2a***	***Stratum 2b****
No G-CSF used	G-CSF used	No G-CSF use	G-CSF used
**Strata 1b and/or 2b will open only if the MTD for the 'a' stratum includes neutropenia*			

O^6-BG will be administered intravenously over 1 hour at a dose of 120mg/m^2, followed immediately by O^6-BG 30 mg/m^2/day for 48 hours. Temozolomide will be administered orally, in a fasting state, no sooner than 6 hours after the end of the one hour bolus infusion of O^6-BG. Temozolomide dosing will begin at 267 mg/m^2. The temozolomide dose will be increased in approximately 33% increments in subsequent cohorts until the MTD is reached.

Objectives:

Primary:

1. To determine the maximum tolerated dose of temozolomide when administered with O^6-benzylguanine with and without G-CSF support to pediatric patients with refractory brain tumors stratified by previous radiotherapy.

Secondary:

1. To characterize the pharmacokinetics of temozolomide and O^6-BG when used in combination.
2. To characterize toxicities associated with the combination of O^6-BG and temozolomide with and without G-CSF support.
3. To document antitumor response in patients when treated with O^6-BG and temozolomide.
4. To determine the levels of MGMT enzyme and mismatch repair (MMR) proteins in tumor tissue, investigating a possible correlation with patient outcome.

Rationale:

The combination of O^6-BG and temozolomide should increase the therapeutic index of temozolomide based on in vitro and in vivo data with the combination of O^6-BG and nitrosoureas. However, the optimal schedule for using O^6-BG and temozolomide in combination is unknown. Important factors that determine the dose and schedule of O^6-BG are the amount of drug required to maximally deplete the MGMT in the tumor tissue and the time required for regeneration of MGMT in the tumor tissue.

Eligibility Criteria:

Recurrent or refractory pediatric brain tumors. A histopathologic diagnosis from either the initial presentation or at the time of recurrence is required for all but brain stem gliomas.

Performance status: Karnofsky or Lansky >= 60%; Life expectancy > 8 weeks.

Neurological Deficits: Patients with neurological deficits should have deficits that are stable for a minimum of 1 week prior to study entry.

Chemotherapy: No more than 2 previous chemotherapy/biologic therapy regimens. Evidence of recovery from prior chemotherapy/biologic therapy. No myelosuppressive chemotherapy within 3 weeks (6 weeks if a nitrosourea agent) of study entry. Patients who have received temozolomide are eligible if they have not received the drug in the past 3 months and did not experience any non–hematopoietic Grade 3/4 toxicity with prior temozolomide therapy.

XRT: > = 3 months prior to study entry for craniospinal irradiation (>= 18 Gy); >= 4 weeks for local radiation to primary tumor; and >= 2 weeks prior to study entry for focal irradiation to symptomatic metastatic sites.

Bone Marrow Transplant: >= 6 months prior to study entry.

Anti-convulsants: Patients will be eligible for this study even if they are receiving anti-convulsants.

Growth factors: Off all colony forming growth factor(s) > 2 weeks prior to study entry (G-CSF, GM-CSF, Erythropoietin).

Dexamethasone: Patients who are receiving dexamethasone must be on a stable dose for at least 1 week prior to study entry.

Contact:

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