

Protocol Abstract

Description:

A phase II study of temozolomide (TMZ), combined with the AGT inhibitor, O⁶-Benzylguanine (O⁶-BG), will be performed in pediatric patients with recurrent or progressive high-grade gliomas or brainstem tumors to determine the activity of this drug combination in this patient population. O⁶-BG will be administered as a 60-minute intravenous (IV) infusion daily for 5 days of a 28-day course. TMZ capsules will be administered orally, 30 minutes after completion of each O⁶-BG infusion.

Objectives:

Primary Objective

1. To estimate the sustained objective response rates to the combination of intravenous O⁶-Benzylguanine (O⁶-BG) and oral temozolomide (TMZ) in children with recurrent or progressive high-grade gliomas and recurrent or progressive brainstem tumors.

Secondary Objectives

1. To further describe the toxicity of the combination of O⁶-BG and TMZ in children with high-grade gliomas and brainstem gliomas.
2. To evaluate changes in MR spectroscopic patterns, MR diffusion and MR perfusion in children with refractory or recurrent high-grade gliomas or brainstem gliomas who are treated with the combination of O⁶-BG and TMZ.

Inclusion Criteria:

- Patients must have a high-grade glioma (including e.g. histologically confirmed anaplastic astrocytoma, glioblastoma multiforme, anaplastic oligodendroglioma, anaplastic ganglioma, gliosarcoma) or a brainstem tumor (histologic confirmation waived) with documentation of disease recurrence or progression after prior therapy.
- Patients must have bi-dimensionally measurable disease, defined as at least one lesion that can be accurately measured in at least two dimensions. Diffuse meningeal involvement is not considered measurable disease.
- **Prior/Concurrent Therapy:** Patients must have received standard therapy, including radiation therapy (if radiation therapy is considered standard treatment for primary or “salvage” therapy in advance of a phase II regimen for the respective disease and presentation). Patients with no more than two recurrences or progressions are eligible.
 - Patients must have recovered from the toxic effects of all prior therapy before entering this study. Recovery is defined as a toxicity grade < 2, using CTCAE v. 3.0, unless otherwise specified in the Inclusion and Exclusion Criteria.
 - **Chemotherapy:** Patients must have:
 - received their last dose of known myelosuppressive anticancer chemotherapy or biological therapy ≥ (3) weeks prior to registration
 - received their last dose of nitrosourea ≥ six (6) weeks prior to study registration

- received their last dose of other investigational agent or an anticancer drug known to not be myelosuppressive \geq seven (7) days prior to study registration.
- Patients who have received prior temozolomide are eligible except as noted in section 4.2.1.
- **Radiation:** Patients must have:
 - receive their last fraction of craniospinal irradiation \geq twelve (12) weeks prior to registration
 - received their last fraction of local irradiation to primary tumor \geq twelve (12) weeks prior to registration.
- **Bone Marrow Transplant:** Patients must be:
 - \geq six (6) months since allogeneic bone marrow transplant
 - \geq three (3) months since autologous bone marrow/stem cell transplant.
- **Growth Factors:** Patients who have received filgrastim, sargramostim, or erythropoietin must be off of these agents for \geq two (2) weeks prior to eligibility labs.
- **Age:** Patients must be \leq 21 years of age.
- **Performance Status:** Karnofsky Performance Scale (for >16 years) or Lansky Performance Score (for \leq 16 years of age) \geq 60 assessed within two (2) weeks prior to registration.
- **Bone Marrow Function:** Patients must have adequate bone marrow function defined as a peripheral absolute neutrophil count of $> 1500/\text{mm}^3$, hemoglobin >8 gm/dL (may be supported), an absolute lymphocyte count $\geq 500/\text{mm}^3$ and a platelet count $> 100,000/\text{mm}^3$ (unsupported).
- **Renal Function:** Patients must have an age-adjusted normal serum creatinine OR a creatinine clearance > 60 mL/min/1.73 m².
- **Hepatic Function:** SGPT and SGOT up to 2.5 upper limit of normal; total bilirubin up to 1.5 times upper limit of normal.
- Because the effects of the combination of O⁶-BG and TMZ on the developing fetus are unknown, female patients of childbearing potential must have a negative serum or urine pregnancy test prior to registration. Female patients must avoid breast-feeding while on this study.
- Patients of childbearing and child-fathering potential must be willing to use a medically acceptable form of birth control, which includes abstinence, while being treated on this study.

Exclusion Criteria

- Patients who have had severe toxicity (defined as \geq Grade 3 CTCAE v 3.0) at least probably attributed to prior temozolomide use.
- Patients receiving any other anticancer or experimental drug therapy, with the exception of corticosteroids.

- Patients with uncontrolled clinically significant systemic illness, including infection or overt renal, hepatic, cardiac or pulmonary disease. Patients with known HIV disease are ineligible.
- Patients with a history of hypersensitivity to dacarbazine, temozolomide, or polyethylene glycol (PEG) are ineligible.

Rationale:

Temozolomide has demonstrated activity in adults with anaplastic astrocytoma, yet no significant activity has been demonstrated with TMZ alone in pediatric high-grade gliomas or brainstem tumors. Since many brain tumors express the repair protein, AGT, this may be a mechanism of drug resistance in this patient population. O⁶-BG irreversibly inactivates and depletes AGT. The combination of O⁶-BG with TMZ may therefore increase efficacy of TMZ in this patient population.