

00-C-0105: A Phase I Trial and Pharmacokinetic Study of Temozolomide and O⁶Benzylguanine in Childhood Solid Tumors

Temozolomide (TMZ) is a prodrug that spontaneously degrades to the active metabolite, MTIC, under physiologic conditions. MTIC is an alkylating agent that preferentially methylates the O⁶-position on guanine. The DNA repair protein, O⁶-alkylguanine-DNA alkyltransferase (AGT) removes the methyl group from the O⁶-position of guanine, repairing the lesion produced by MTIC. AGT is expressed in many tumors and has been associated with tumor resistance and poor clinical response to methylating agents, such as the nitrosoureas and temozolomide. O⁶-Benzylguanine (O⁶BG) is an AGT substrate that permanently inactivates AGT. O⁶BG depletes tumor AGT, blocks repair of the lesion produced by temozolomide and thereby enhances its cytotoxicity.

ELIGIBILITY CRITERIA:

Age: Patients must be ≤ 21 years of age.

Histological diagnosis: Patients must have a histologically confirmed solid tumor, which may include, but is not limited to, rhabdomyosarcoma and other soft tissue sarcomas, Ewing's family tumors, osteosarcoma, neuroblastoma, Wilms' tumor, hepatic tumors, germ cell tumors or primary brain tumor. For patients with brainstem gliomas or optic gliomas, the requirement for histological confirmation may be waived.

Prior therapy:

- The patient's tumor must be refractory to standard treatment. Patients must have no known potentially curative therapy available to them. Curative therapy may include surgery, radiation therapy, chemotherapy, or any combination of these modalities.
- Patients must have had their last dose of limited-field radiation therapy at least four weeks prior to study entry. Patients who have received extensive prior radiation therapy (craniospinal radiation, total body radiation, or radiation to more than half of the pelvis) must be at least 4 months post-completion of radiation therapy. Patients must have received their last dose of chemotherapy at least three weeks prior to study entry (four weeks for nitrosoureas), and their last investigational therapy at least four weeks prior to study entry.
- Patients must have recovered from the toxic effects of all prior therapy prior to entry onto this trial.
- Patients with brain tumors who are receiving corticosteroids for the control of tumor-associated edema must be on a stable or decreasing dose for at least 1 week prior to study enrollment.
- Patients who have previously received temozolomide are eligible if they have not received the drug in the past 3 months and they did not experience severe toxicities during their previous course of therapy with temozolomide. Severe toxicity is defined as any grade 4 non-hematologic toxicity or failure to recover (to grade ≤ 1 level) from any non-hematologic or hematologic toxicity within six weeks of receiving temozolomide. Patients who received temozolomide in combination with other agents that were designed to inactivate AGT are not eligible for this trial.
- Patients should be off colony stimulating factors such as G-CSF, GM-CSF, and Epo for at least one week prior to study entry.

Measurable/Evaluable disease: Patients must have measurable or evaluable disease. There must be evidence of progressive disease on prior chemotherapy or radiation therapy or persistent disease after surgery.

Performance status: Patients should have an ECOG performance status of 0, 1, or 2 (see Table below) and a life expectancy of at least eight (8) weeks. Patients who are unable to walk because of paralysis, but who are up in a wheel chair will be considered ambulatory for the purpose of calculating the performance score.

ECOG Performance Status

Score	Clinical Status
0	Asymptomatic
1	Symptomatic, fully ambulatory
2	Symptomatic, in bed < 50% of the day
3	Symptomatic, in bed > 50% of the day but not bedridden
4	Bedridden

Hematological function: Patients must have adequate bone marrow function defined as a peripheral absolute granulocyte count of $>1500/\text{mm}^3$, hemoglobin $>8 \text{ gm/dL}$, and platelet count $>100,000/\text{mm}^3$.

Hepatic function: Patients must have adequate liver function, defined as bilirubin within normal limits and SGPT $<2x$ the upper limit of normal.

Renal function: Patients must have an age-adjusted normal serum creatinine (see Table below) OR a creatinine clearance $\geq 60 \text{ mL/min/1.73 m}^2$.

AGE (YEARS)	MAXIMUM SERUM CREATININE (MG/DL)
≤ 5	0.8
$5 < \text{AGE} \leq 10$	1.0
$10 < \text{AGE} \leq 15$	1.2
> 15	1.5

Patients must be able to swallow capsules.

Informed consent: All patients or their legal guardians (if the patient is <18 years old) must sign a document of informed consent indicating their understanding of the investigational nature and the risks of this study BEFORE any protocol related studies are performed (this does not include routine laboratory tests or imaging studies required to establish eligibility). When appropriate, pediatric patients will be included in all discussions in order to obtain verbal assent.

Durable Power of Attorney (DPA): Assignment of DPA to a family member or guardian should be offered to all patients 18 to 21 years of age who have a brain tumor.

EXCLUSION CRITERIA

- Patients currently receiving other investigational chemotherapeutic agents.
- Patients with a history of myeloablative therapy requiring bone marrow or stem cell transplantation within the previous 4 months.
- Pregnant or breast-feeding females are excluded because this regimen is known to have mutagenic effects in vitro and may therefore have detrimental effects on a developing fetus or newborn.
- Clinically significant unrelated systemic illness (serious infections or significant cardiac, pulmonary, hepatic or other organ dysfunction) which in the judgment of the Principal or Associate Investigator would compromise the patient's ability to tolerate this therapy or are likely to interfere with the study procedures or results.
- Patients with a history of hypersensitivity to dacarbazine, temozolomide, or polyethylene glycol (PEG).

PRETREATMENT EVALUATION:

- History and physical, neurological exam for patients with brain tumors, documentation of signs and symptoms and measurable disease, height, weight, BSA

- Laboratory work to assess blood counts, organ function and metabolic status within 72 hours prior to enrollment
- Radiologic evaluation within the 2 weeks prior to start of therapy
- Quality of Life assessment: IPI questionnaire for patient and parent
- Patients should bring to NIH summaries of previous treatment, most recent laboratory work, copies of most recent radiologic studies that document disease progression from last treatment, and original pathology slides and report and tissue blocks.

GENERAL TREATMENT PLAN:

- A combination of intravenous O⁶BG given over one hour followed by oral TMZ will be administered daily for 5 consecutive days every 28 days. This trial will follow a two-part dose-escalation design (O⁶BG will be escalated first and TMZ will be escalated once the optimal O⁶BG dose is reached) in an attempt to define the maximum tolerated dose of TMZ that can be administered with a biologically active dose of O⁶BG. Intra-patient dose escalation of TMZ will occur if it was tolerated on the prior cycle.

PHARMACOKINETICS:

- Blood samples will be drawn on the first cycle after the fifth doses of O⁶BG/TMZ. Sixteen samples will be collected in total. A 10 ml blood sample will be collected on Days 1, 3 & 5 of Cycle 1 to measure levels of AGT in PBMCs in patients >40 kg with WBC >400/mm³.

HOSPITALIZATION:

- Patients will be treated as an outpatient, unless clinically contraindicated

ACCRUAL:

- This trial is open to accrual. Patients meeting eligibility criteria can be referred to the Pediatric Oncology Branch, NCI, for evaluation and treatment. Patients should bring to NIH a summary of previous treatment, most recent laboratory work, copies of most recent radiologic studies including 2 scans that document disease progression from last treatment, and original pathology slides and report.