Full Title
Open-Label Phase I/Phase II Study of Intravenous Infusion of Tetra-o-Methyl Nordihydroguaiaretic Acid (EM-1421) in Subjects with Recurrent High Grade Glioma

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Objectives
Phase I

Primary Objective: To determine the maximum tolerated dose (MTD) of Tetra-O-Methyl Nordihydroguaiaretic Acid (EM-1421) administered as a daily intravenous infusion for 5 consecutive days every 28 days to adults with recurrent high grade glioma, receiving anticonvulsants that induce hepatic metabolic enzymes (Group A) or not receiving anticonvulsants or receiving anticonvulsants with modest induction or no induction of hepatic metabolic enzymes (Group B).

Secondary Objectives:

1. To describe the pharmacokinetics of this route of administration, measuring EM-1421, and to determine the effects of hepatic enzyme-inducing drugs, anticonvulsants, on the pharmacokinetics.
2. To estimate the toxicity and to assess the tolerability associated with EM-1421.
3. To assess the anti-tumor activity in terms of overall survival.

Phase II

Primary Objective: To estimate the response rates of adult patients with recurrent high grade glioma treated with EM-1421 administered at the MTD.
Secondary Objectives:

1. To assess overall survival.
2. To assess the safety and tolerability associated with the EM-1421 given at the MTD in patients with recurrent high grade glioma.

Eligibility

Inclusion

1. Patients must be at least 18 years of age.
2. Patients must have histologically proven malignant glioma (anaplastic astrocytoma, anaplastic oligodendroglioma or glioblastoma multiforme) which is progressive or recurrent after radiation therapy ± chemotherapy. Patients with previous low grade glioma who progressed after radiotherapy ± chemotherapy and are biopsied and found to have a high grade glioma are eligible.
3. Patients must have contrast enhancing measurable progressive or recurrent malignant glioma by MRI or CT imaging. (Within 14 days before starting treatment).
4. Patients must have recovered from toxicity of prior therapy. An interval of at least 3 months must have elapsed since the completion of the most recent course of radiation therapy, while at least 3 weeks must have elapsed since the completion of a non-nitrosourea containing chemotherapy regimen, and at least 6 weeks since the completion of a nitrosourea containing chemotherapy regimen. NOTE: For a non-cytotoxic, FDA approved agents (i.e. celebrex, thalidomide, etc.) therapy could be started 2 weeks after discontinuing this agent provided the patient has fully recovered from all toxicity associated with the agent. For investigational, non-cytotoxic agents a minimum of 3 weeks must have elapsed before the patient will be eligible for this study.
5. Patients must have a Karnofsky performance status > 60% (i.e. the patient must be able to care for himself/herself with occasional help from others).
6. Patients must have normal hematologic, renal and liver function. Patients must meet the following laboratory criteria:
   - absolute neutrophil count > 1500/mm$^3$;
   - hemoglobin > 9 gm/dl;
   - platelets > 100,000/mm$^3$;
   - creatinine < 1.5mg/dl;
7. Patients must be able to provide written informed consent.
8. Patients with the potential for pregnancy or impregnating their partner must agree to follow acceptable birth control methods to avoid conception. Women of childbearing potential must have a negative serum pregnancy test. (The anti-proliferative activity of this experimental drug may be harmful to the developing fetus or nursing infant.)
9. Patients must have a Mini Mental State Exam score > 15.

Exclusions

1. Patients with serious concurrent infection or medical illness which would jeopardize the ability of the patient to receive the treatment outlined in this protocol with reasonable safety.
2. Patients who are pregnant or breast-feeding. (The anti-proliferative activity of this experimental drug may be harmful to the developing fetus or nursing infant.)
3. Patients receiving concurrent therapy for their tumor (with the exception of steroids).
4. Patients with a concurrent malignancy are ineligible unless they are patients with curatively treated carcinoma-in-situ or basal cell carcinoma of the skin. Patients with a prior malignancy are ineligible unless they have been free of disease for > five years.
5. Patients with a known sensitivity to any of the study medication components (EM-1421 is formulated in a solution of Polyethylene glycol (PEG 300) and 2-Hydroxypropyl β-cyclodextrin).