Protocol Abstract and Schema

A Phase I Trial of Capecitabine Rapidly Disintegrating Tablets and Concomitant Radiation Therapy in Children with Newly Diagnosed Brainstem Gliomas and High Grade Gliomas

Description:

Children with newly diagnosed, diffuse intrinsic brain stem gliomas and high grade gliomas are eligible for this protocol. During the dose-finding period, oral Capecitabine Rapidly Disintegrating Tablets (Capecitabine RDT) will be administered daily in two divided doses approximately 12 hours apart beginning within 24 hours of the start of radiation therapy (conventional or conformal volume-based external beam radiation therapy). Oral capecitabine RDT will continue for a total of nine weeks, followed by a two-week break. Post-RT therapy will begin after the two week break. Post radiation therapy, patients will receive twice daily oral capecitabine for 3 courses. During each course, capecitabine will be administered for 14 consecutive days followed by a 7-day rest period.

Capecitabine will be provided as a flavored, film coated, rapidly disintegrating tablet that may be swallowed intact or dispersed in water for patients unable to swallow tablets. The starting capecitabine dose will be 80% of the MTD for capecitabine administered concurrently with radiation in adults with high-grade gliomas (HGG). Subsequent dose-escalations will be in increments of 30% using a standard dose escalation schema. The dose-limiting toxicity (DLT) observation (dose-finding) period begins with the first dose of capecitabine RDT and ends two weeks following the completion of radiation therapy or with the occurrence of a DLT, whichever comes first.

Efficacy will be assessed by MRI scans with and without contrast enhancement. Safety evaluations will include routine clinical and neurological examinations, evaluation of symptomatic adverse events, and laboratory studies including CBCs, electrolytes, and assessments of renal and hepatic function. Adverse events will be reported and graded according to V.3 of the NCI Toxicity Criteria.

Pharmacokinetics will be evaluated for each consenting patient.

Primary Objectives:

1. To estimate the maximum tolerated dose (MTD) of capecitabine administered concurrently with radiation therapy (RT) to children with newly diagnosed non-disseminated, intrinsic brainstem gliomas or newly diagnosed non-disseminated high-grade gliomas.

2. To describe the dose-limiting toxicity (ies) of capecitabine administered concurrently with radiation therapy to children with newly diagnosed non-disseminated, intrinsic brainstem gliomas or newly diagnosed non-disseminated high-grade gliomas.

Secondary Objectives:

3. To characterize the pharmacokinetics of capecitabine as delivered by Capecitabine Rapidly Disintegrating Tablets in this pediatric patient population.

4. To describe in the context of this phase 1 investigation, the anti-tumor activity of capecitabine and radiation that is observed in children with newly diagnosed non-disseminated, intrinsic brainstem gliomas or newly diagnosed non-disseminated high-grade gliomas.

5. To characterize radiographic changes in brainstem gliomas treated with radiation and capecitabine using MRI, MRS, perfusion and diffusion imaging and PET scans.

Eligibility Criteria:

- **Age:** Patient must be ≥ 3 and ≤ 21 years of age.

- **Tumor**: Patients must have one of the following tumors.

  - Brainstem glioma (non-disseminated): Newly diagnosed non-disseminated intrinsic infiltrating brainstem glioma. Histopathologic diagnosis is not required.
  - High-grade glioma (non-disseminated): Patients must have a histopathologic diagnosis of a newly diagnosed, incompletely resected, non-disseminated high-grade glioma (anaplastic astrocytoma, glioblastoma multiforme or other high-grade glioma). Patients with an anaplastic oligodendroglioma are not eligible. There must be evidence of residual measurable tumor on post-operative MRI or CT.
  - Patients with HGG must be registered within 28 days of definitive surgery.

- **Performance status:** Karnofsky Performance Scale (if > 16 yrs) or Lansky Performance Score (if < 16 years) ≥ 50% assessed within two weeks prior to registration.

- **Prior/Concurrent therapy:** Patients must not have received any prior chemotherapy, radiation therapy, immunotherapy or bone marrow transplant. Prior dexamethasone and/or surgery are allowed.

- **Organ function:** Patients with adequate organ function as defined by the following parameters obtained within two (2) weeks prior to registration and again within seven (7) days prior to the start of therapy. Eligibility labs need not be repeated if therapy starts within 7 days of drawing labs.

  - Bone marrow: Absolute Neutrophil Count (ANC) ≥ 1,000/mm^3; Platelets ≥ 100,000/ mm^3 (transfusion independent); Hemoglobin ≥ 8 g/dl (transfusion independent)

  - Renal: Creatinine clearance or radioisotope GFR ≥ 70 ml/min/1.73m2 or a serum creatinine based on age as follows:

Age (years)	Maximum Serum Creatinine (mg/dL)
< 5	0.8
5 < age < 10	1
10 < age < 15	1.2
>15	1.5

  - Hepatic: Bilirubin ≤ 1.5x normal institutional normal for age; SGPT (ALT) ≤ 5x institutional upper limits of normal for age.

- **Birth control:** Patients of childbearing or child fathering potential must be willing to use a medically acceptable form of birth control, which includes abstinence, while being treated on this study.

- **Consent:** Signed informed consent according to institutional guidelines must be obtained prior to study entry.

Exclusion Criteria:

- Patients receiving any other anticancer or experimental drug therapy.

- Patients with uncontrolled infection.

- Patients with significant cardiac, hepatic, gastrointestinal, renal, pulmonary, or other systemic disease

- Patients with a known hypersensitivity to capecitabine or any of its components

- Patients with known dihydropyrimidine dehydrogenase (DPD) deficiency.

- Patients who are receiving any of the following medications: warfarin, sorivudine or chemically related analogues, such as brivudine.

- Patients who are pregnant and/or lactating.

Schema:

- **Dose finding:** Capecitabine will be given orally daily in two divided doses approximately 12 hours apart, beginning within 24 hours of the start of radiation therapy and continuing for 9 weeks. Patients will have a two-week break following the completion of the 9-week course of capecitabine prior to the initiation of Post RT phase. It is anticipated that it will take approximately 6 weeks to deliver the prescribed radiation therapy dose (Section 6.0). This entire 11-week period is Dose finding.

- **Post RT Phase:** Post radiation therapy with capecitabine will begin after the completion of the two-week break during Dose finding. During Post RT, patients will receive twice daily oral capecitabine for a total of 3 courses. Each course is defined as 14 consecutive days of capecitabine followed by a 7-day rest period.

- **Starting Capecitabine Dose**: The starting dose of capecitabine during radiation will be 500 mg/m2 bid, which is 80% of the adult maximum tolerated dose (625 mg/m^2 bid). Subsequent dose-escalations will be in increments of 30%. There should be no interruptions in the absence of dose limiting toxicity. Each 21-day period is defined as a course. (**Note**: The dose post-RT is different than the dose during radiation.)

Capecitabine Schedule		
Dose finding	**Weeks**	**Protocol Therapy**
Course 1	Weeks 1 through 3	Capecitabine + RT
Course 2	Weeks 4 through 6	Capecitabine + RT
Course 3	Week 7 through 9	Capecitabine $\pm$ RT*
Break	Weeks 10 and 11	None
Post RT phase		
Course 4	Weeks 1 and 2 Week 3	Capecitabine None
Course 5	Weeks 4 and 5 Weeks 6	Capecitabine None
Course 6	Weeks 7 and 8 Weeks 9	Capecitabine None

* Patients who did not complete radiation as planned at the end of week 6, will continue to receive radiation during course 3 to complete the prescribed radiotherapy dose.

Dose finding Capecitabine Escalation Table		
Dose Level	**Dose bid (mg/m^2/dose)**	**Total Daily Dose (mg/m^2/day)**
0	375	750
1*	500	1000
2	650	1300
3	850	1700
Post RT Capecitabine Dose		
0	900	1800
1*	1250	2500

* Starting dose