

ACNS0821: Temozolomide With Irinotecan Versus Temozolomide, Irinotecan Plus Bevacizumab (NSC# 704865, BB-IND# 7921) for Recurrent/Refractory Medulloblastoma/CNS PNET of Childhood, A COG Randomized Phase II Screening Trial

Type	Status	Age Range	Sponsor	Protocol ID
Interventional	Active	1 – 21 yrs	CCHMC	ACNS0821

Purpose

This randomized phase II trial is studying how well giving temozolomide and irinotecan hydrochloride together with or without bevacizumab works in treating young patients with recurrent or refractory medulloblastoma or CNS primitive neuroectodermal tumors.

Rationale

Drugs used in chemotherapy, such as temozolomide and irinotecan hydrochloride, work in different ways to stop the growth of tumor cells, either by killing the cells or by stopping them from dividing. Monoclonal antibodies, such as bevacizumab, can block tumor growth in different ways. Some block the ability of tumor cells to grow and spread. Others find tumor cells and help kill them or carry tumor-killing substances to them. It is not yet known whether temozolomide and irinotecan hydrochloride are more effective with or without bevacizumab in treating medulloblastoma or CNS primitive neuroectodermal tumors.

Objectives

Primary

- To compare the overall survival (OS) of subjects receiving the combination of temozolomide and irinotecan with that of subjects receiving temozolomide, irinotecan, and bevacizumab for recurrent medulloblastoma (MB)/PNET of childhood.

Secondary

- To assess the response rate for each treatment arm.
- To determine event-free survival (EFS) for each patient compared across regimens.

Outline

This is a multicenter study. Patients are randomized to 1 of 2 treatment arms.

Arm I

Patients receive oral temozolomide and irinotecan hydrochloride IV over 90 minutes on days 1-5.

Arm II

Patients receive oral temozolomide and irinotecan hydrochloride IV as in arm I and bevacizumab IV over 30-90 minutes on days 1 and 15.

In both arms, treatment repeats every 28 days for up to 12 courses in the absence of disease progression or unacceptable toxicity.

After completion of study treatment, patients are followed up for 5 years.

Eligibility

Up to 21 years

Disease Characteristics

- Diagnosis of medulloblastoma or PNET of childhood that has relapsed or become refractory to standard chemotherapy
- Patients must have experienced at least one and at most two relapses prior to study enrollment
 - Patients with primary refractory disease are eligible
- Patients must have had histologic verification of the malignancy at original diagnosis or at the time of recurrence
- Patients must have measurable residual disease, defined as tumor that is measurable in two perpendicular diameters on MRI
 - Diffuse leptomeningeal disease is not considered measurable
- All patients must have a brain MRI with and without gadolinium and a spine MRI with gadolinium performed within 2 weeks prior to study enrollment
 - Patients must not have evidence of new CNS hemorrhage on baseline MRI

Patient Characteristics

- Patients must have a Lansky or Karnofsky performance status score of $\geq 50\%$, corresponding to ECOG categories of 0, 1, or 2 (Karnofsky for patients > 16 years of age and Lansky for patients ≤ 16 years of age)
- Patients must have a life expectancy of ≥ 8 weeks
- Peripheral absolute neutrophil count (ANC) $\geq 1000/\mu\text{L}$ (must not have received G-CSF within the prior 7 days)
- Platelet count $\geq 100,000/\mu\text{L}$ (transfusion independent)
- Hemoglobin ≥ 8.0 g/dL (may receive PRBC transfusions)
- Creatinine clearance or radioisotope GFR ≥ 70 mL/min/1.73m² OR a serum creatinine based on age/gender as follows:
 - ≤ 0.4 mg/dL (for patients aged 1 month to < 6 months)
 - ≤ 0.5 mg/dL (for patients aged 6 months to < 1 year)
 - ≤ 0.6 mg/dL (for patients aged 1 to < 2 years)
 - ≤ 0.8 mg/dL (for patients aged 2 to < 6 years)
 - ≤ 1 mg/dL (for patients aged 6 to < 10 years)
 - ≤ 1.2 mg/dL (for patients aged 10 to < 13 years)
 - ≤ 1.4 mg/dL (for female patients aged ≥ 13 years)

- ≤ 1.5 mg/dL (for male patients aged 13 to < 16 years)
- ≤ 1.7 mg/dL (for male patients aged ≥ 16 years)
- Urine protein should be screened by dipstick analysis
 - If protein $\geq 2+$ on dipstick, then urine protein creatinine (UPC) ratio should be calculated
 - If UPC ratio > 0.5 , 24-hour urine protein should be obtained and the level should be $< 1,000$ mg/24 hours for patient enrollment
- Total bilirubin ≤ 1.5 x upper limit of normal (ULN) for age
- SGPT (ALT) ≤ 3 x ULN for age
- INR/PT ≤ 1.5 x ULN
- Female patients who are pregnant are not eligible for this study
- Female patients who are breastfeeding are not eligible for this study unless they agree not to breastfeed
- Female patients of childbearing potential must have a negative pregnancy test
- Sexually active patients of childbearing potential must agree to use an effective method of contraception during the study and for at least 6 months after the completion of bevacizumab therapy
- Hypertension must be well controlled (≤ 95 th percentile for age and height if patient is ≤ 17 years) on stable doses of medication
- Patients with a seizure disorder may be enrolled if well-controlled and on non-enzyme inducing anticonvulsants
- Patients with a serious or non-healing wound, ulcer, or bone fracture are not eligible for this study
- Patients must not have a history of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within 6 months prior to study entry
- Patients must not have a known bleeding diathesis or coagulopathy
- Patients must not have had significant vascular disease (e.g., aortic aneurysm requiring surgical repair, deep venous or arterial thrombosis) within the last 6 months prior to study entry
- Patients must not have a known thrombophilic condition (i.e., protein S, protein C or antithrombin III deficiency, Factor V Leiden, Factor II G20210A mutation, homocysteinemia, or antiphospholipid antibody syndrome)
 - Testing is not required in patients without thrombophilic history
- Patients with a history of stroke, myocardial infarction, transient ischemic attack (TIA), severe or unstable angina, peripheral vascular disease, or grade II or greater congestive heart failure within the past 6 months are not eligible
- Patients must not have serious and inadequately controlled cardiac arrhythmia
- No patients with known hypersensitivity to Chinese hamster ovary cell products or other recombinant human antibodies

Prior Concurrent Therapy

- See Disease Characteristics
- Patients must have fully recovered from the acute toxic effects of all prior chemotherapy, immunotherapy, or radiotherapy prior to entering this study\
- No myelosuppressive chemotherapy within 3 weeks of entry onto this study (6 weeks if prior nitrosourea)
- At least 7 days since the completion of therapy with a biologic agent; at least 3 weeks for biologic agents with a long half life, such as antibodies
- Must not have received craniospinal radiotherapy within 24 weeks prior to study entry or involved-field radiotherapy to the local tumor (and/or tumor designated as "measurable" for protocol purposes within 12 weeks prior to study entry); focal radiation to areas of symptomatic metastatic disease must not be given within 14 days of study entry
- For autologous stem cell transplant, ≥ 3 months must have elapsed prior to study entry
- Patients must not have previously received bevacizumab, irinotecan, temozolomide, or other anti-VEGF inhibitor

- Patients must not be taking enzyme-inducing antiepileptic medicines within 1 week of study entry
- Patients must have recovered from any surgical procedure before enrolling on this study
 - Patients with a major surgical procedure within 28 days prior to beginning therapy should be excluded
 - Patients with an intermediate surgical procedure within 14 days prior to beginning therapy should be excluded
 - For minor surgical procedures (including Broviac line or infusaport placement), patients should not receive the first planned dose of bevacizumab until the wound is healed and at least 7 days have elapsed (lumbar punctures or placement of PICC lines are not considered minor procedures and may occur at any time prior to or during therapy)
 - There should be no anticipation of need for major surgical procedures during the course of the study
- No growth factors within 7 days of entry onto this study
- Patients who are receiving corticosteroids must be on a stable or decreasing dose for at least 7 days
- Patients must not be currently taking NSAIDs, clopidogrel, dipyridamole, or aspirin therapy > 81 mg/day
- No other cancer chemotherapy or immunomodulating agents are permitted (the use of alternative or complementary therapies is discouraged)
- No concurrent radiotherapy

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