

01-C-0123 A Phase II Study of Intrathecal Topotecan (NSC #609699) in Patients with Refractory Meningeal Malignancies

This protocol is a Children's Oncology Group-wide trial. Topotecan is an FDA approved anticancer agent that inhibits topoisomerase I and has activity in solid tumors. From our phase I trial of intrathecal topotecan 0.4 mg was a safe dose in children and adults. The objectives of this multi-institutional phase II study are to determine the response rate and time to CNS progression with intrathecal topotecan in patients with recurrent or refractory leptomeningeal spread of tumors and to further assess the safety and toxicity of intrathecal topotecan.

ELIGIBILITY CRITERIA:

Age: Patients must be ≥ 1 and ≤ 21.99 years of age at study entry.

Diagnosis: Patients must have neoplastic meningitis. Patients with meningeal leukemia/lymphoma must be refractory to conventional therapy (i.e., 2nd or greater relapse). The definition of neoplastic meningitis on this protocol is as follows:

- Leukemia/Lymphoma: CSF cell count $> 5/\text{ul}$ AND evidence of blast cells on cytopspin preparation or by cytology.
- Solid Tumors/Other: Presence of tumor cells on cytopspin preparation or cytology OR presence of meningeal disease on MRI scans.

Life Expectancy: Patients must have a life expectancy of at least 8 weeks.

Performance Status: Patients > 10 y.o. should have Karnofsky performance status of $\geq 50\%$ and patients ≤ 10 y.o. should have a Lansky performance status of $\geq 50\%$. (See Appendix II.) Patients who are unable to walk because of paralysis, but who are up in a wheel chair, will be considered ambulatory for the purposes of the performance score.

Recovery from Prior Therapy: Patients must have recovered from the acute toxic effects of all prior chemotherapy, immunotherapy, or radiotherapy, prior to entering this study and must be without significant systemic illness (e.g. infection). Patients must not have received any systemic CNS-directed therapy within 3 weeks (6 weeks if a prior nitrosourea), or craniospinal irradiation within 8 weeks prior to starting treatment on this study. Patients must not have received intrathecal chemotherapy within 1 week (2 weeks if prior DTC101). Patients who have had IT chemotherapy, e.g. in the - 7 to - 14 day period prior to study entry must have evidence of disease progression, e.g. increasing WBC and percentage blasts in patients with leukemia/lymphoma or increased leptomeningeal enhancements in patients with solid tumors.

Hematologic Status: Patients must have a platelet count $> 40,000/\text{ul}$, with transfusions allowed to achieve this platelet count, within 48 hours prior to intrathecal topotecan treatment.

Organ Function: Patients must have adequate liver function, total bilirubin < 2.0 mg%; SGPT < 5 times normal; adequate renal function (serum creatinine < 1.5 mg); and normal metabolic parameters (serum electrolytes, calcium and phosphorus).

Informed Consent: All patients or their legal guardians must sign a written informed consent according to institutional guidelines.

Protocol must have a current local full board IRB approval, including active amendments requiring full board IRB approvals expire in 365 days from the initial local IRB approval.

EXCLUSION CRITERIA:

- Patients receiving other therapy (either intrathecal or systemic) designed specifically to treat their leptomeningeal disease are not eligible for this study. However, patients receiving concomitant chemotherapy to control systemic disease or bulk CNS disease will be eligible, provided the systemic chemotherapy to control systemic disease or bulk CNS disease will be eligible, provided the systemic chemotherapy is not a phase I agent, an agent which significantly penetrates the CSF (e.g., high-dose methotrexate (>1 gm/m²), thiotepa, high-dose cytarabine, 5-fluorouracil, intravenous 6-mercaptopurine, nitrosoureas, or topotecan), or an agent known to have serious unpredictable CNS side effects. Careful documentation of concurrently administered systemic drugs is required.
- Patients with a ventriculoperitoneal (VP) or ventriculoatrial (VA) shunt are not eligible for this study unless they are shunt independent and there is evidence that their shunt is nonfunctional; e.g., a CSF flow study demonstrating normal flow.
- Patients with leukemia/lymphoma who have a concomitant bone marrow relapse are not eligible for this study.
- Women of childbearing age must not be pregnant or lactating because of potential teratogenic effects (e.g. The anti-proliferative activity of the investigational agent may be harmful to the developing fetus or the nursing infant.
- Free of uncontrolled infection except HIV (i.e., AIDS-related lymphomatous meningitis.).
- Use of any other investigational drug within 7 days prior to study entry. This period should be extended if the patient has received any investigational agent which is known to have delayed toxicities after 7 days or a prolonged half-life.
- Patients with impending cord compression, CNS involvement requiring local XRT (e.g. optic nerve), or isolated bulky ventricular or leptomeningeal based lesions are not eligible for this study.

PRETREATMENT EVALUATION:

- History and physical examination, including a detailed neurological exam, CBC, chemistries
- Drug may be administered by intralumbar injection or through a ventricular access device, e.g., Ommaya reservoir
- CSF studies: CSF cell count, differential, protein, and glucose within 72 hrs prior to treatment. Cytospins should be performed in patients with leukemia/lymphoma and cytopathology is required for solid tumor patients. Patients, who have signed the consent to allow CSF sampling for MMP concentration, will have the unused portion of the CSF, that is routinely drawn, sent to TXCH for analysis of MMP. The sampling timepoints include: prior to therapy, at completion of induction and consolidation, every two months during maintenance and every 4 months after completion of maintenance.
- Bone marrow aspirate (within 2 weeks prior to study entry) for all patients with leukemia/lymphoma and as indicated for solid tumor patients
- Radiographic studies (within 2 weeks prior to protocol entry)
- Nuclear medicine studies (within 2 weeks prior to protocol entry) Pre-treatment radionuclide CSF flow study is required for patients with leukemia or lymphoma if CSF blockage is suggested.

GENERAL TREATMENT PLAN:

- Patients will receive intrathecal topotecan on a twice weekly schedule for a total of 6 weeks. If no evidence of disease progression patients continue to consolidation and maintenance schedules. Drug administration may be either by the intraventricular or intralumbar route. Patients must remain flat for at least 1 hour following administration of an intralumbar dose.

ACCRUAL:

- Patients meeting eligibility criteria can be referred to the Pediatric Oncology Branch, NCI for evaluation and treatment or to any COG institution.