90-C-0095: Phase I Study of Intrathecal Mafosfamide

This protocol is coordinated by Texas Children's Hospital. The purpose is to determine optimal dose of intrathecal (IT) mafosfamide, a preactivated derivative of cyclophosphamide, against meningeal malignancies refractory to conventional therapy. The optimal dose will be established in a limited dosage escalation schedule in patients with refractory meningeal disease.

ELIGIBILITY CRITERIA:

Age: All patients over 3 years of age with meningeal malignancies that are progressive or refractory to conventional therapy will be eligible for this study. Patients with meningeal malignancies secondary to an underlying solid tumor are eligible at initial diagnosis if there is no conventional therapy.

Diagnosis: Patients with leukemia, lymphoma, or other solid tumor who also have overt meningeal involvement by their tumor. The definition of meningeal disease on this protocol includes:

- Leukemia/Lymphoma - CSF cell count ≥ 5/mm^3 AND evidence of blast cells on cytospin preparation or by cytology.
- Solid tumors - Presence of tumor cells on cytospin preparation or cytology OR presence of measurable meningeal disease on CT or MRI scans.

Life Expectancy: of at least 8 weeks.

Performance Status: ECOG performance status of 2 or better. Patients who are unable to walk because of paralysis, but who are up in a wheelchair will be considered ambulatory for the purposes of the performance score.

Informed Consent: Patients and/or their parents must sign an informed consent indicating that they are aware of the investigational nature of this study.

Prior Therapy: Patients must have recovered from the acute toxic effects of all prior intrathecal 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 CNS therapy within 1 week prior to starting treatment on this study 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).

Laboratory Results: Patients must not have clinically significant abnormalities with regard to liver function, renal function or metabolic parameters (electrolytes, calcium and phosphorus).

Durable Power of Attorney (DPA): A DPA must be offered to all patients ≥ 18 years of age.

EXCLUSION CRITERIA:

- Patients receiving other therapy (either intrathecal or systemic) designed specifically to treat their meningeal malignancy are not eligible for this study. However, patients receiving concomitant chemotherapy to control systemic or bulk CNS disease will be eligible, provided the systemic chemotherapy is not a phase I agent, an agent which significantly penetrates the CNS (e.g., high dose methotrexate, (> 1 gm/m^2), thiotepa, high dose cytarabine, (> 2 gm/m^2 per day), 5-fluorouracil, intravenous 6-mercaptopurine or topotecan), or an agent known to have serious unpredictable CNS side effects. Careful documentation of systemic drugs being administered concurrently is required. (Please discuss systemic plans for systemic therapy with the principal investigator prior to study entry).
- Patients with clinical evidence of obstructive hydrocephalus or compartmentalization of the CSF flow as documented by a radioisotope Indium^{111} or Technitium^{99}-DTPA flow study are not eligible for this protocol. If a CSF flow block or compartmentalization is demonstrated, focal radiotherapy to the site of block to restore flow and a repeat CSF flow study showing clearing of the blockage is required for the patient to be eligible for the study.
- Patients who have leukemia or lymphoma and a concomitant bone marrow relapse are not eligible for this study.
- Women of childbearing age must not be pregnant or lactating.
- Patients must not have received any other systemic investigational agent within 14 days prior to, or during, study treatment. The 14 day period should be extended if the patient received any investigational agent which is known to have delayed toxicities after 14 days. Patients must not have received any other intrathecal investigational within 7 days prior to, or during, study treatment. The 7 day period should be extended if the patient received any investigational agent which is known to have delayed toxicities after 7 days or a prolonged half-life.

PRE-TREATMENT EVALUATION:

- History and physical exam and laboratory work (see protocol). DPA has to be offered to patients ≥ 18 years of age.
- Lumbar puncture and Ommaya tap (in patients with Ommaya reservoirs)
- Bone marrow evaluation for leukemia/lymphoma pts and when clinically indicated in solid tumor pts within 3 wks of protocol entry
- Head CT or MRI. CT mylogram or MRI of the spine, with & without contrast for all patients with nonleukemic/lymphomatous leptomeningeal disease and others as clinically indicated.
- ^{111}In DTPA scan or ^{99m}Tc-DTPA scan for all solid tumors. A pretreatment radionucliide CSF flow study is also required for patients with leukemia or lymphoma if CSF analysis suggests a CSF blockage.

- Patients should bring to the NIH summaries of previous treatment, most recent laboratory work including CSF results, most recent bone marrow slides, most recent CSF slides, copies of most recent CT/MRI, and original pathology slides and reports.

GENERAL TREATMENT PLAN:

- Initially treatment is twice weekly for 6 weeks. When possible, doses are alternated between Ommaya reservoir and lumbar puncture. Patients without an Ommaya will receive all doses via intralumbar route. Further therapy will be based on CSF cell counts/imaging studies. Patients benefiting from induction therapy receive an additional 4 weekly doses, then every other week x 8 doses, then monthly maintenance. Drug is given over 20 minutes via infusion pump to prevent pain. Patients are also premedicated with analgesics.

PHARMACOKINETICS:

- CSF pharmacokinetic studies will be performed with a total of 2 doses of intrathecal mafosfamide (after one intraventricular dose and after one intralumbar dose) in patients who have Ommaya reservoirs. Samples are collected prior to drug administration and at 15 min, 30 min, 1 hr, 2 hrs, 3 hrs, 5 hrs and 8 hrs, following drug administration. Following intraventricular dosing only, a lumbar CSF sample should be obtained for a mafosfamide drug level at 2 hours following drug administration.

OPEN TO ACCRUAL:

- Patients meeting the eligibility criteria can be referred to the Pediatric Oncology Branch, NCI for evaluation and treatment. Other participating institutions include the Mayo Clinic, Children's Hospital of Los Angeles, and Children's Hospital National Medical Center of D.C., MD Anderson Cancer Center of Houston, Texas Children's Hospital and Children's Hospital and Medical Center, Seattle.