

**92-C-0137: A Trial of Carboxypeptidase-G<sub>2</sub> (CPDG<sub>2</sub>) for the Management of Patients with Intrathecal Methotrexate Overdose**

Methotrexate is the most widely used intrathecal antineoplastic agent. Accidental IT overdose, usually the result of inadvertent IT injection of a higher dose intended for systemic administration, can produce severe and frequently lethal toxicity. Current therapeutic approaches are invasive and often ineffective. Carboxypeptidase-G<sub>2</sub>, an enzyme that hydrolyzes the C-terminal glutamate residue from MTX, may potentially serve as a rescue agent for patients suffering from potentially lethal IT MTX overdoses. This trial will study the ability of a single IT injection of CPDG<sub>2</sub> to rescue patients with IT MTX overdose.

**ELIGIBILITY CRITERIA:**

**IT MTX Overdose:** Any patient who receives an IT overdose of MTX  $\geq 100$  mg will be eligible for the study.

**Informed Consent:**

- An IT overdose of MTX constitutes a medical emergency. IRBs of participating centers may therefore choose to waive the requirement for obtaining written informed consent prior to administration of CPDG<sub>2</sub>.
- A participating IRB may choose not to waive the requirement for written informed consent. Should a participating IRB choose to waive this requirement, a verbal explanation of the investigative nature should be provided to the patient or parent/guardian when feasible prior to administration of CPDG<sub>2</sub>.
- Written informed consent to (1) inform the patient or patient's family that the drug has been administered and describe what may be expected, and (2) to permit additional lumbar punctures for pharmacokinetic studies, should be obtained from the patient or the parent/guardian as soon as feasible after the administration of CPDG<sub>2</sub>.

**EXCLUSION CRITERIA**

- Patients who have previously developed an anaphylactic reaction to prior CPDG<sub>2</sub> administration are ineligible.
- There will be no exclusions based on concurrent therapy.

**PRE-TREATMENT EVALUATION:**

- History and physical exam, including a detailed neurological exam
- Height, weight and body surface area should be recorded
- CSF Methotrexate concentration, including documentation of the time elapsed from the MTX dose

**GENERAL TREATMENT PLAN:**

- A repeat lumbar puncture should be performed as soon as possible after the IT MTX overdose. CSF must flow freely and should be drained by gravity for approximately 5 minutes.
- A single dose of 2000 units of CPDG<sub>2</sub> in the age appropriate volume of normal saline (see protocol) should be administered intrathecally over 5 minutes.
- Supportive care recommendations (emergency neurosurgical consultation for possible ventriculo-lumbar perfusion, systemic administration of leucovorin, systemic administration of decadron) are outlined in the protocol.

**PHARMACOKINETICS:**

- CSF for Methotrexate determination will be obtained immediately prior to, and 60 minutes and 24 and 48 hours after administration of CPDG<sub>2</sub>. Collection of CSF should be performed as described in Appendix 1b of the protocol. 5 ml of plasma should also be obtained at 3, 7, and 14 days following enzyme administration for determination of CPDG<sub>2</sub> antibody levels.

**TOXICITY/ACCRUAL:**

- Six patients have received IT CPDG<sub>2</sub> for an accidental IT MTX overdose to date. The drug has been well tolerated, and resulted in a marked decrease in CSF MTX concentrations.

**COMPASSIONATE-USE:**

- CPDG<sub>2</sub> for compassionate use can be obtained from the Cancer Therapy Evaluation Program of the National Cancer Institute by calling: 301-496-5725.