

99-C-0088: ¹H-Nuclear Magnetic Resonance Spectroscopic Imaging of the Brain in Patients Who Receive Neurotoxic Therapy

¹H-NMRS is a noninvasive method of obtaining in vivo biochemical information from the brain. It has been used to study patients with CNS disorders, including neuronal disorders. In this study, ¹H-NMRS will be used to objectively characterize CNS toxicities in patients with cancer who are receiving potentially neurotoxic therapies. In addition, we will retrospectively evaluate patients with known or suspected neurotoxicity associated with cancer therapy, to determine if changes in spectroscopic patterns are associated with CNS toxicity.

ELIGIBILITY CRITERIA:

INCLUSION CRITERIA

Diagnosis or Treatment: Patients with brain tumors or patients receiving high-dose systemic chemotherapy, intrathecal chemotherapy (lumbar puncture or intra-Ommaya), or cranial radiation therapy OR patients with documented or suspected clinical neurotoxicity presumed to be caused by treatment for cancer.

Durable Power of Attorney (DPA): should be offered to all patients greater than or equal to 18 years of age.

Informed Consent: All patients or their legal guardians (if the patient is < 18 years of age) must sign a document of informed consent indicating their awareness of the investigational nature and the risks of this study. When appropriate, the minor patient will sign a written assent.

EXCLUSION CRITERIA

- Pregnancy (The effects from the magnet on the fetus are unknown. In addition, gadolinium is not approved for use in pregnant women, because its teratogenic effects have not been studied).
- Patients with braces or permanent retainers (These metallic devices interfere with obtaining adequate spectroscopy).
- Patients with pre-existing neurologic or genetic conditions, unrelated to the tumor (It will not be possible to distinguish the spectroscopy pattern produced by the underlying, pre-existing condition from the effects of the treatment with methotrexate or radiation).
- Patients who are unable (either because of physical or psychological factors) to undergo imaging studies and who are not a candidate for anesthesia.
- Patients who have an absent gag reflex or swallowing difficulties.
- Metallic implant, including cardiac pacemakers, neural pacemakers, aneurysmal clips, shrapnel, cochlear implants or ferrous surgical clips.
- History of severe reaction to Gadolinium.

PRETREATMENT EVALUATION:

- History and physical, including a neurologic examination.
- Pregnancy test in females of child-bearing potential.
- Anesthesia consult and evaluation for patients who will require sedation or anesthesia for imaging and spectroscopy studies.
- Baseline neuropsychologic testing if possible.
- Patients should bring to NIH summaries of previous treatment, copies of radiologic studies, and all neuropsych testing results.

GENERAL PLAN:

- NMRS studies will be performed on patients at any or all of the following times: prior to therapy, immediately after the first cycle of therapy, prior to subsequent cycles of therapy, or after completion of all therapy. Neurotoxicity will be quantified by neuropsychologic testing.

ACCRUAL:

- Open to accrual.
- Patients meeting the eligibility criteria can be referred to the Neuro-Oncology Branch, NCI (Dr. Kathy Warren at 301-402-6298) for evaluation and on this trial.

Emergency Access to IV Carboxypeptidase-G₂ for High-Dose Methotrexate-Induced Renal Dysfunction

CPDG₂ and thymidine are available for intravenous administration through a "compassionate-use protocol" from the Cancer Therapy Evaluation Program (CTEP) of the National Cancer Institute.

DETERMINE ELIGIBILITY OF PATIENT BASED ON THE PROTOCOL ENTRY CRITERIA:

ENTRY CRITERIA

MTX Toxicity and Age: Patients of any age who are at risk for life-threatening toxicity following MTX administration secondary to delayed drug excretion as defined by:

- Plasma MTX concentration $\geq 10 \mu\text{M}$ more than 42 hours after the start of the MTX infusion (or)
- Creatinine ≥ 1.5 times the upper limit of normal or creatinine clearance $\leq 60 \text{ ml/m}^2/\text{min}$ and delayed MTX excretion documented by plasma MTX concentration measurements (≥ 2 standard deviations above the mean) at least 12 hours following MTX administration.

RESCUE REGIMEN FOR PATIENTS WITH DELAYED MTX EXCRETION FROM HIGH-DOSE MTX NEPHROTOXICITY:

Treatment with CPDG₂, leucovorin, (and thymidine)

- **CPDG₂** will be administered at a dose of 50 units/kg x 1 dose intravenously over 5 minutes. Patients with plasma MTX concentrations $>100 \mu\text{M}$ immediately prior to CPDG₂ administration will receive a second dose of CPDG₂ 48 hours after administration of the first dose.
- **Thymidine** will only be administered to patients who already suffer from severe MTX toxicity at the time NIH is contacted, including grade 3 or 4 mucositis, absolute neutrophil count $<1,000/\mu\text{L}$, or platelet count $< 50,000/\mu\text{L}$. Greater than grade 2 diarrhea, nausea, vomiting, or increase in liver function tests are not reasons to administer thymidine. Thymidine will be administered as a 24-hour continuous intravenous infusion at a dose of 8 grams/m²/day, and will be continued for 48 hours after administration of the last dose of CPDG₂.
- **Leucovorin** should administered at a dose of 1000 mg/m² IV q6 hours. Though LV is a weak substrate for CPDG₂, it may compete with MTX and, if possible, should therefore not be administered 2 hours prior to and for 2 hours following the administration of CPDG₂. Following the administration of the CPDG₂, LV rescue should be continued at a dose of 250 mg/m² IV every six hours for a total of 48 hours. After that time LV rescue should be adjusted based on plasma MTX concentrations determined by the institutional assay. LV administration should be continued until serum MTX concentrations are less than 0.05 μM .

SHOULD YOUR PATIENT BE ELIGIBLE, PLEASE MAKE SURE THAT THE LEUCOVORIN DOSE IS ADEQUATE (1,000 MG/M² IV EVERY 6 HOURS), AND THAT THE PATIENT CONTINUES WITH ALKALINIZATION AND HYDRATION, PROVIDED HIGH URINE OUTPUT CAN BE MAINTAINED.

- Should the patient be clearly ineligible for the trial, please guide the physician from the outside institution regarding the further management (LV rescue, etc).
- Should you be uncertain regarding the patient eligibility, please call CTEP. The pharmacists there have a lot of experience with the protocol, and will be able to make this decision.

CALL THE PHARMACEUTICAL MANAGEMENT BRANCH AT CTEP: CTEP WILL NEED THE FOLLOWING INFORMATION:

- Your name, phone number and shipping address, the patient's initials, age, weight, dose and schedule of MTX, date and time MTX was administered, baseline and current serum creatinine, current MTX level and time level was drawn, and description of current MTX related toxicities (mucositis, bone marrow suppression, dermatitis, liver function tests).
- The phone number is 301-496-5725.
- During working hours (8:30 AM to 4:30 PM) you will reach the receptionist. Please tell her you emergently need CPDG₂, and she will guide you to the right person.
- After working hours and on weekends, call the same phone number: 301-496-5725. There will be a recording telling you that nobody can take your call. This is followed immediately by a message telling you how to proceed should you have an urgent need for CPDG₂. You will be guided through the process of leaving a message.
- Pharmacist Michelle Washart, or the on-call pharmacist from CTEP will call you back shortly. Relate the information to CTEP. CTEP will organize shipment of CPDG₂ and the protocol.