

Protocol # 97-C-0093: 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.

1) Determine eligibility of patient based on the Protocol Entry Criteria:

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.

2) 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 .

3) 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 alkalization 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.

4) 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.
- 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.

5) Should you get no response from CTEP (this has not happened so far, provided you leave a clear message including your phone number to call back with your message), please call Aiman Shalabi (Responsible pharmacist at CTEP for this protocol): Home phone number - 301-896-0035; Cell phone - 301-613-8350; Office phone number - (301) 435-9088.