

Reduced-Dose Carboxypeptidase-G2 Successfully Lowers Elevated Methotrexate Levels in an Adult With Acute Methotrexate-Induced Renal Failure

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Introduction

Methotrexate (MTX), an antifolate agent widely used for the treatment of lymphoid malignancies, is primarily eliminated through the kidneys. Renal dysfunction, which can occur during administration of high-dose MTX (HDMTX) (generally defined as $>1 \text{ gm/m}^2$ of body surface area), results in delayed elimination and excessive accumulation of MTX within tissues.¹ It is currently unclear whether leucovorin rescue (LVR) alone, which is routinely administered after HDMTX infusion, is sufficient to prevent toxicity from sustained high-level MTX exposure. High-flux hemodialysis (HHD) has been shown to successfully reduce MTX levels, but generally requires multiple dialysis sessions, with attendant morbidity and cost.^{2,3} Carboxypeptidase-G2 (CPG2), also known as glucarpidase (Voraxaze, BTG International Ltd), cleaves MTX to inactive metabolite, rapidly reducing MTX levels to nearly undetectable within minutes.^{4,5} This agent was recently approved by the US Food and Drug Administration (FDA) for the treatment of HDMTX-induced renal toxicity. CPG2 is generally well tolerated, but is extremely expensive when administered at the approved dose.⁶ Current Centers for Medicare and Medicaid Services guidelines limit reimbursement to costs associated with approximately half of the FDA-approved dose. Herein we report a case of HDMTX-induced renal toxicity in a patient who was successfully treated with CPG2 at approximately one-sixth of the FDA-approved dose.

Case Report

The patient was a 59-year-old man with newly diagnosed pre-T acute lymphoblastic lymphoma. He received cycle 1 (part A) hyper-CVAD (fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone) without adverse effects. At the time of initiation of hyper-CVAD (part B), baseline chemistries, liver function, lactate dehydrogenase, and white blood cell count (WBC) were all within normal limits. Baseline serum creatinine (Scr) was 0.91 mg/dL. Allopurinol 300 mg daily and hydration with sodium bicarbonate infusion (150 mL/hr) was initiated before the HDMTX infusion. MTX 2 g/m^2 (4,100 mg) was given as a continuous infusion over 24 hours (day 1). Leucovorin 25 mg every 6 hours was started 12 hours after infusion was completed. Twenty-four hours after initiation of MTX, Scr increased to 2.58 mg/dL with reduced urine output. Over the next 48 hours (days 3 and 4), Scr increased to 4.54 mg/dL, and the patient became anuric. Bicarbonate infusion was discontinued due to fluid retention and metabolic alkalosis. MTX levels showed delayed elimination and remained elevated ($>5 \text{ }\mu\text{M}$) for over 96 hours. The calculated MTX elimination rate constant (K_e) decreased more than 30-fold during this time (0.418 hr^{-1} to 0.012 hr^{-1}). The leucovorin dose was increased to 100 mg/m^2 every 6 hours per the dosing algorithm, and HHD was performed on day 5. Twenty-four hours after the first HHD session, K_e was nearly identical to the day prior to HHD (0.016 hr^{-1} vs 0.012 hr^{-1}), with essentially no change in serum MTX level. A second HHD session was performed on day 6. MTX levels were drawn immediately after the second HHD session, which showed significant improvement in both MTX levels ($1.2 \text{ }\mu\text{M}$) and K_e (0.09 hr^{-1}) compared to the first HHD session. However, given the discordant MTX levels and K_e measurements observed between the

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first and second dialysis sessions, we conjectured that the second post-HHD MTX level may have been falsely low, perhaps because it was drawn prior to a new steady-state MTX level, and also did not account for the significant rebound in MTX levels routinely observed 24 hours after dialysis.^{2,3} A decision was made to treat the patient with a single 1,000-unit dose of CPG2 (approximately 15% of the approved dose). A serum MTX level, drawn 12 hours after CPG2 was administered, showed a dramatic decrease to 0.5 μM . At that point, HHD was discontinued, and no further CPG2 doses were given. MTX levels continued to steadily decline, and renal function slowly improved over the next 5 days. No delayed signs of MTX toxicity were observed. The patient was discharged on day 11 (Scr, 2.4; MTX level, 0.07; WBC, 2.6) and was able to complete the next course of chemotherapy with minimal delay.

Discussion

To our knowledge, this is the first case report of successfully lowering MTX levels with a markedly reduced CPG2 dose in an adult. Results from clinical experience with conventional-dose CPG2 show a 2-logarithm decrease in MTX levels within 15 minutes of administration. We hypothesized that a reduced CPG2 dose, when allowed to circulate for several hours, would reduce MTX levels 1 logarithm or more, to serum levels that then could be managed with LVR alone (below approximately 1 μM). Our reported experience appeared to confirm this. It should be noted that the extent to which CPG2 lowered MTX levels may have been significantly underestimated, as the MTX immunoassay used to determine MTX levels at our institution measures both parent MTX as well as inactive 4-diamino-N10-methylpteroic acid (DAMPA) metabolite (which may equal pre-CPG2 MTX levels). Whether this reduction in MTX level prevented MTX toxicity is unknown, as the patient received concomitant LVR.

The management of HDMTX-induced renal toxicity remains challenging. HDMTX displays concentration-time-dependent pharmacokinetics, requiring replenishment of reduced folate with LVR in order to prevent potentially life-threatening bone marrow suppression and mucosal toxicity. MTX toxicity does not become clinically apparent until several days after MTX administration. Early intervention may reduce the risk for MTX toxicity and also increase the likelihood of remaining adherent to the treatment schedule.

Current treatment strategies include administration of pharmacokinetically-guided LVR, hemodialysis, hemo-perfusion, administration of CPG2, or combinations of these modalities. From the standpoint of preventing potential MTX toxicity, CPG2 reduces MTX to safe levels

almost instantaneously, whereas HHD dialysis improves MTX levels in a slower fashion (9–14 sessions).^{2,3} LVR is dependent on the return of normal renal function to eliminate MTX, and this recovery may take several weeks. Furthermore, when serum MTX concentrations are sustained above 10–100 μM , high-dose LVR is not likely to effectively prevent MTX toxicity.⁷ Some investigators have suggested the following risk stratification for the treatment of MTX-induced renal toxicity: patients with sustained MTX levels greater than 10 μM measured 42–48 hours after MTX infusion should receive CPG2; whereas patients with MTX levels ranging from 1–10 μM should initially be managed with LVR alone, and CPG2 or other modalities should be considered for sustained MTX exposure.⁸

Cost is a major barrier for CPG2 treatment. The average cost for a single 1,000-unit vial is approximately \$22,500.⁸ The FDA-approved dose is 50 $\mu\text{g}/\text{kg}$, which would cost more than \$88,000 for an average-sized male patient. Our patient weighed 130 kg and would therefore have required 7 vials (estimated total cost, >\$155,000) as a single dose, according to dosing guidelines. Reduced-dose CPG2 lowered drug cost by 85% in our patient, and limited HHD to 2 sessions. Current guidelines from the Centers for Medicare and Medicaid Services allow for the reimbursement of only 2 CPG2 vials, which would be approximately half of the FDA-approved dose for patients of average body mass.⁹ Future pharmacoeconomic studies are required in order to determine whether the cost of reduced-dose CPG2 is offset by the reduction in both HHD and length of hospital stay.

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Review

Using a Lower Dose of Glucarpidase to Reduce Plasma Levels of Methotrexate

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Introduction

Methotrexate (MTX) is a widely used anti-cancer agent. Administration of high doses of MTX (HDMTX) followed by leucovorin rescue has been incorporated into the treatment of several childhood and adult cancers. For patients with normal renal function, HDMTX can be administered safely with appropriate supportive care, including vigorous hydration and alkalinization to enhance the solubility of the drug, and pharmacokinetically-guided leucovorin rescue.¹ In spite of these optimal supportive care measures, HDMTX-induced renal toxicity continues to develop in a small subset of patients and represents a medical emergency, as more than 90% of MTX is cleared by renal excretion.² In addition to conventional treatments, carboxypeptidase-G₂ (glucarpidase [Voraxaze, BTG International Ltd]), a bacterial enzyme which hydrolyzes MTX to inactive metabolites, provides an alternate route of MTX elimination. It has become available and was approved by the US Food and Drug Administration (FDA) in January 2012 for the treatment of toxic plasma MTX concentrations in patients with impaired renal function at a dose of 50 units/kg administered intravenously as a bolus injection.

In their report, Trifilio and associates³ describe a patient with acute lymphoblastic leukemia who developed renal dysfunction after administration of HDMTX. In addition to conventional measures, high-flux hemodialysis (HHD) was instituted, with limited effectiveness. Approximately 7 days after the start of HDMTX, glucarpidase (1,000 units) was administered, corresponding to approximately 8 units/kg of body weight. The plasma MTX concentration measured with an immunoassay decreased from approximately 1.2 μ M pre-glucarpidase to 0.5 μ M after glucarpidase. The patient recovered from toxicities and was able to receive

further MTX. The authors concluded that glucarpidase, when administered in lower doses than what is approved by the FDA, can result in clinically meaningful MTX reductions, and highlight this finding in view of the substantial cost of glucarpidase.

Discussion

The authors describe a successful outcome of HDMTX-induced renal dysfunction with administration of glucarpidase at a reduced dose. A few points are worth highlighting.

In previously reported studies, glucarpidase was documented to result in a decrease in plasma MTX concentrations that was rapid (within 15 minutes) and profound (median decrease in plasma MTX concentrations >97%).^{4,5} In contrast, dialysis-based methods of MTX removal are invasive and were found to be less effective.² Prior studies also document that the greatest benefit of glucarpidase administration is to be expected when glucarpidase is administered early (within 96 hours of initiation of MTX administration).⁵ The patient described in this report underwent HHD prior to receiving glucarpidase approximately 1 week after MTX, at a time when plasma MTX concentrations had already declined substantially. While the indication for HHD is not detailed by Trifilio and colleagues, earlier administration of glucarpidase could have been considered and might have obviated the need for HHD.

The approximately twofold to threefold reduction in plasma MTX concentrations observed in this patient must be interpreted with caution, as an immunoassay was used for quantification. Immunoassays, which are most commonly used to determine plasma MTX concentrations in the clinical setting, demonstrate cross reactivity with inactive MTX metabolites and thus result in substantial overestimation of post-glucarpidase MTX concentrations.⁶ A specific and sensitive method of plasma MTX determination, such as high-pressure liquid chromatography (HPLC), is required in order to accurately determine plasma MTX after glucarpidase. In absence of a specific assay for MTX, the recommendation is to continue leucovorin rescue based on measurements with the local assay, even though this likely results in higher leucovorin doses than needed.

The authors discuss that the patient received a substantially lower dose than what is recommended in the package label. Glucarpidase is dosed based on body weight. However, glucarpidase has a large molecular weight and thus does not gain intracellular access, and is only expected to hydrolyze MTX in the blood. The patient described in this report was substantially overweight (130 kg), but likely had a similar blood volume to that of an average adult, which should be taken into

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consideration. Schwartz and coworkers also reported a subset of 11 patients who were unable to receive full doses of glucarpidase due to a drug shortage. These patients received glucarpidase in doses ranging from 10–31 units/kg, with no different effect on MTX toxicity or pharmacokinetics compared to patients who received the full dose.⁴

Cost of glucarpidase is an important factor to consider, as emphasized by the authors. However, prospective studies evaluating the effect of lower doses of glucarpidase on plasma MTX concentrations have not been reported to date. These studies should be conducted, ideally with HPLC monitoring, prior to considering a change in dose due to drug expense.

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