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Practical Considerations for the Administration of Glucarpidase in High-Dose Methotrexate (HDMTX) Induced Renal Dysfunction

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High-dose methotrexate (HDMTX) induced renal dysfunction is a medical emergency, as MTX is primarily eliminated by renal excretion.[1] In spite of optimal supportive care including vigorous hydration, alkalinization, and pharmacokinetically guided leucovorin rescue, approximately 1.8% of patients with osteosarcoma enrolled on clinical trials develop HDMTX-induced renal dysfunction,[2] and this incidence may be higher in subgroups of patients, for example, in older patients.[3] Patients with sustained exposure to elevated plasma MTX concentrations are at greatest risk for the development of potentially life-threatening MTX related toxicities, in particular myelosuppression and mucositis. Dialysis-based methods have been widely used in the past to mechanically remove MTX, but with limited efficiency.[2] Glucarpidase is a bacterial enzyme that results in a rapid, profound, and sustained decrease in plasma MTX concentrations by hydrolysis of MTX to inactive metabolites. In clinical studies, early administration of glucarpidase at a time when plasma MTX concentrations were high was found to provide the greatest benefit.[4–6] In 2012, the FDA approved the use of glucapridase for plasma MTX concentrations ≥1 μM in the presence of renal impairment at a single dose of 50 U/kg as an intravenous bolus over 5 min. The approval of glucapridase eliminates the need for use of dialysis-based methods of MTX removal and allows for noninvasive, effective, and rapid removal of methotrexate within minutes of administration. However, the substantial cost of glucapridase has resulted in reevaluation of the dose of glucapridase that is required to achieve the desired decrease in plasma MTX concentrations.

In this issue, Scott et al. provide data that glucarpidase doses lower than 50 U/kg results in equivalent plasma MTX reduction compared to the FDA approved dose.[7] Their study was prompted by the substantial cost of glucapridase ($27,000 per 1,000 unit vial), and the fact that current Centers for Medicare and Medicaid Services guidelines allow for reimbursement of only 2 glucapridase vials per administration. In their analysis of 26 patients, who had received glucapridase for HDMTX-induced renal dysfunction, doses less than 50 U/kg were the result of capping the dose at a full size vial. The median glucarpidase dose was 50.8 U/kg (range,13.0–90.0 U/kg), and 42% of the patients received a glucapridase dose less than 50 U/kg. There were no statistically significant differences in decreases in plasma MTX concentrations measured by HPLC or by fluorescence polarization immune assay (TDx) or

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in the time to recovery of renal function for patients who received doses less than 50 U/kg or ≥50 U/kg. The authors suggest rounding the glucapridase dose down to the nearest vial size as one approach to safely reduce the cost of gucarpidase and describe that their institution has now adopted capping of the glucapridase dose at two vials (2,000 U), the dose allowed for reimbursement. Using this approach all patients ≤40 kg body weight would receive the FDA approved dose, and all patients with a body weight ≥41 kg would receive a fixed capped dose of 2,000 U.

The authors address a clinically very relevant question, and while their analysis is retrospective, it supports that lower glucapridase doses than 50 U/kg can achieve equivalent decreases in plasma MTX concentrations compared to the FDA approved dose. The authors also provide useful considerations for dose reductions of glucapridase given the current level of reimbursement. Other reports have described successful rescue with lower doses of glucapridase.[4,8] In the largest series next to the one reported by Scott et al. in this issue, Schwartz et al. reported a subset of 11 adult patients, who received glucapridase doses ranging from 10 to 31 U/kg with no different effect on MTX toxicity or pharmacokinetics compared to patients who received the full dose.[4] The FDA approved dose of 50 U/kg was used in all clinical studies leading to drug approval, and in the absence of prior studies assessing the relationship of varying doses of glucapridase and the decrease in plasma MTX concentrations, a prospective study analyzing plasma MTX concentrations following lower doses of glucapridase is required to establish the validity of this approach. While most institutions follow plasma MTX concentrations with immunoassays such as the TDx assay used by Scott et al., these assays demonstrate cross reactivity with inactive MTX metabolites and thus result in substantial overestimation of post glucapridase MTX concentrations.[9,10] Specific and sensitive methods of MTX determination, such as high-pressure liquid chromatography should therefore ideally be used in prospective studies to accurately determine plasma MTX after glucapridase administration.[6]

Another consideration to reduce the cost of glucapridase could be to limit the administration of gucarpidase to patients at greatest risk for the development of MTX toxicity even with optimal supportive management.[11] This would include patients with plasma MTX concentrations ≥10 μM at 42–48 hr after start of the MTX infusion. While some of these patients can be rescued with optimal supportive care alone,[12] they remain at great risk for severe MTX toxicity for as long as elevated concentrations of MTX persist in circulation, a risk, which can be rapidly eliminated with the timely administration of gucapridase. Preclinical studies support this by demonstrating that when concentrations of MTX reach 100 μM, even 10-fold higher LV concentrations (1,000 μM) were unable to protect bone marrow cells from toxicity.[13] In addition to the plasma MTX concentration, other factors such as the degree of renal dysfunction, patient age, concomitant medications, and MTX toxicities present at the time of diagnosis should factor into the decision to administer glucapridase.

Future studies will allow further defining the required dose of glucarpidase and its role in the treatment of HDMTX induced renal dysfunction.

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