Advances in Managing Acute Kidney Injury:
Improving Outcomes for Patients Treated with High-Dose Methotrexate

Case Study 1: HDMTX-Induced AKI in Osteosarcoma

Nancy Nix: Hello and welcome to Advances in Managing Acute Kidney Injury: Improving Outcomes for Patients Treated With High-Dose Methotrexate—a two-part educational series for oncology advanced practitioners. I am Nancy Nix, clinical assistant professor for the University of Georgia College of Pharmacy, and I am joined by my colleague Kristi Posey.

Kristi Posey: I am Kristi Posey, physician assistant in sarcoma medical oncology at MD Anderson Cancer Center. Nancy, thanks for having me.

Nancy Nix: Thank you for joining us. In this video, we will be discussing strategies for monitoring patients with acute kidney injury following treatment with high-dose methotrexate, which may occur at doses of 500 mg/m^2 or greater. We will utilize the case of an adult female with osteosarcoma, her associated demographics, baseline clinical and laboratory characteristics, and accompanying glucarpidase treatment to demonstrate the best available evidence and updated guidelines.

Nancy Nix: Before we dive into the case study, let's talk briefly about high-dose methotrexate–induced acute kidney injury. High-dose methotrexate is used in several regimens for patients with solid tumors and hematologic malignancies. Some patients experience delayed methotrexate excretion and prolonged exposure to toxic methotrexate concentrations, which can lead to significant morbidity and mortality without timely recognition and treatment. Despite appropriate supportive care measures during the administration of high-dose methotrexate, acute kidney injury develops in up to 12% of patients, with a mortality rate of 6%. Kristi, can you give a brief overview of adult osteosarcoma?

Kristi Posey: Absolutely. Osteosarcoma is a primary cancer of bone. It is often inherently high grade with a propensity to metastasize to the lungs. It is more common in children and young adults, but can occur in the older populations. It has a predisposition for the distal femur, the proximal tibia, and the proximal humerus. High-dose methotrexate is part of a first-line chemotherapy combination regimen often used

for children. It is the M in the MAP therapy. However, it is also an active adjuvant therapy for poor responders in adults. High-dose methotrexate–induced renal dysfunction continues to occur in approximately 1.8% of patients with osteosarcoma treated in clinical trials. The mortality among patients who develop renal dysfunction is 4.4%.

Nancy Nix: What are identifiable risk factors to assess before administering high-dose methotrexate?

Kristi Posey: There are about four or five readily identifiable risk factors that you can attempt to combat before you give this therapy. The first one is already established baseline chronic kidney disease or extensive comorbidities – the likelihood of reduced renal function resulting from the physiological aging processes as well as the acquisition of comorbidities increases with age. While there is no comparable overview on the adults and elderly patients that exists, there is some available data that does indicate that the incidence of high-dose methotrexate–related nephrotoxicity may be considerably higher in this subgroup of patients.

Kristi Posey: The second is addressing pretreatment volume depletion. So this coincides with the theory that the etiology of methotrexate-induced renal dysfunction is believed to be mediated by the precipitation of methotrexate and its metabolites within the renal tubules or via a direct toxic effect of the methotrexate on the renal tubules. So having proper prehydration can, therefore, attempt to protect these renal tubules from this precipitation. So we will often use IV hydration at 2.5 to 3.5 L/m^2 per 24 hours beginning 12 hours before the methotrexate infusion and then continuing for 24 to 48 hours.

Kristi Posey: The third is addressing any pretherapy acidic urine. So, if you think that, more than 90% of methotrexate is cleared by the kidneys, and methotrexate is poorly soluble at an acidic pH as well as it metabolites. If you neutralize or increase the urine pH from 6 to 7, this in itself can result in a 5- to 10-fold greater solubility of the methotrexate and its metabolites. So this is the finding that underlies the entire standard recommendation of urine alkalinization. So we will normally use 40 to 50 mEq of sodium bicarbonate per liter of IV fluid prior to, during, as well as after the administration of high-dose methotrexate.

Kristi Posey: You always need to address any drug interactions that are going to occur between any of the drugs that are provided from the patient at the time of giving the drug. Several drugs have been associated with increased toxicity when co-administered with methotrexate. The most significant interaction involves agents that interfere with methotrexate excretion. This is primarily because it competes for the renal tubular excretion, and this includes the probenecids, the salicylates, the sulfonamides, penicillins, or NSAIDs. And finally any patient that has been heavily pretreated in the neoadjuvant or the palliative setting needs special consideration. Patients in the adult setting especially are often administered high-dose methotrexate after initial neoadjuvant nephrotoxic therapies. So their baseline creatinine statuses have often already been compromised by this point and the toxicity effects can become accumulative.

Nancy Nix: What pretreatment strategies should be utilized for patient home monitoring and education while on high-dose methotrexate?

Kristi Posey: So, at our institution we provide a one-on-one methotrexate preparation score before starting cycle 1 day 1, and this is led by the nursing team, and they will provide the patient with a comparable overview and handouts that include PO hydration at home with a goal of 2 to 3 L PO daily, urine testing strips with pH strips, and home use of sodium bicarbonate. So, they will be instructed that they will have 650 mg tablets of sodium bicarb. They will take four tablets at night the day before they start methotrexate, their day 1 of methotrexate in the morning, and then they will continue it every 6 hours around the clock. As well, they will also take an additional four tablets any time their urine is tested as being less than 7. They are also educated in the initiation of leucovorin rescue at 25 mg that begins exactly 24 hours from the time their methotrexate was started and continuing 6 hours around the clock. Timely lab draws are absolutely vital or essential toxicity screening, so appropriate timing of lab draws is well gone through and educated with the patient. So they are instructed to return to the clinic at the same time at the start of their infusion for their daily methotrexate level, as well as their BUN and creatinine check, which are then reviewed by the triage nurse and the primary team. Lastly, they are given easy warning signs of fevers, chills, intractable nausea, vomiting, decreased PO intake, and any other further need for supportive care via admission.

Nancy Nix: Please share the details of your case study.

Kristi Posey: My case study starts with a 31-year-old white female without a past medical history. She initially presented with a persistent right lower leg pain that became progressive, and on a simple x-ray, she was noted to have a blastic metaphyseal base lesion with associated periosteal elevation. She underwent a core needle biopsy and was noted to have a diagnosis of fibroblastic osteosarcoma. Her initial staging showed localized disease only without any other signs of distant metastasis. So the strategy then was initiated to be neoadjuvant chemotherapy for a goal of response assessment, treatment of presumed micrometastasis, and finally for a goal of curative intent.

Kristi Posey: Okay. She is initiated on a neoadjuvant doublet therapy of dose-optimized doxorubicin at 75 mg/m^2 IV continuous infusion over 72 hours and cisplatin at 120 mg/m^2 over 4 hours IV. This is given inpatient with planned aggressive IV fluids at a rate of 250 mL per hour, and the goal is to give a total of four cycles. Response assessment is obtained every two cycles with a PET-CT with IV contrast, which notes stable volumetric disease with a slight decrease in avidity, which is consistent with a positive response. Surgical resection including a planned limb salvage is timed within 28 days of her fourth doxorubicin/cisplatin regimen. She undergoes a radical resection and endoprosthetic reconstruction with negative margins, but is noted to have a 70% necrosis. So her suboptimal necrosis places her in the category of a poor responder, and she is then initiated on a planned adjuvant course encompassing alternating regimens of high-dose methotrexate followed by single agent high-dose ifosfamide.

Kristi Posey: Now it is important to note that her creatinine status pretreatment, otherwise known as our baseline level before she started any chemotherapy, was 0.4 to 0.5. By the time she had completed her four cycles of doxorubicin and cisplatin, creatinine was 0.85. Therefore, she has already exhibited a 100% increase from her baseline level, which is consistent with cisplatin injury despite the fact that this is within a typical normal limit range and the reference range. So, she is scheduled to start her first outpatient high-dose methotrexate course at a dose of 10 g/m^2 infused over 4 hours. She obtains her optimal pretherapy one-on-one counseling including emphasis on PO hydration at home, urine testing with the pH strips, use of sodium bicarbonate, and the use of leucovorin rescue. Her medications were reviewed for nephrotoxicity and/or drug interactions with the

primary team and our dedicated sarcoma pharmacists as standard practice. She is instructed to return to the clinic at the same time at the start of her infusion every day for her daily methotrexate and BUN/creatinine level, which are then reviewed with the triage nurse and the primary team. She proceeds with cycle 1 day 1 of her infusion, and her methotrexate peak is noted to be 1726.54 µM with an associated clinical fatigue. She proceeds with cycle 1 day 1 of her infusions, and her methotrexate peak is noted to be 1726.54 µM with associated clinical fatigue.

Nancy Nix: Kristi, is that a high level?

Kristi Posey: That is actually well over the therapeutic window. Our goal is normally 1000 µM, so this was considered significantly higher.

Kristi Posey: So now this patient returns the next day for her timely 8:00 a.m. 24-hour lab draw, and at that time her methotrexate level is noted to be 263.76. The triage nurse is also notified that the patient is home with reported lethargy and altered mental status.

Nancy Nix: Kristi, please define what methotrexate level you would typically expect 24 hours after treatment.

Kristi Posey: I will tell you that I do not anticipate anything that high. The standard reference range that we have actually in our lab value system is less than 10 that is usually associated with pediatrics levels. I think what is important here to note is that you want a level that is substantially lower than 50. Per the Ramsay et al consensus guideline, anything over 50 µM should be the first consideration for use of glucarpidase rescue treatments. However, the other thing to watch is what does the patient look like. So this patient clearly has this new change in her performance status, which is one of the most important parts of this that we need to pay attention to – so not only a substantially high level, but clinically there is a significant deterioration.

Nancy Nix: What is an optimal form of patient monitoring to expedite identification of emerging toxicity?

Kristi Posey: Through our consistent standard practice we have found that the team approach has been the best way to obtain a quality picture of the patients. The triage nurse, advanced practice provider, attending physician, and pharmacists are all part of this set of constant communication with regards to patient status changes. This includes combining interpretation of laboratory data as well as a clinical assessment in order to make rapid decisions.

Kristi Posey: At the time of this significant patient's status change, the primary team in the clinic including the advanced practice provider and the attending physician are notified immediately, along with the incoming lab levels. The patient is then instructed to report to our emergency center immediately. Our pharmacist is also simultaneously informed of the high methotrexate level as well as the clinical presentation, and it initiates the needs for approval glucarpidase to be sent to the bedside upon arrival. The total time for decision and planning is less than 5 minutes.

Nancy Nix: Wow, Kristi, that is an amazing response time. So what emergent rescue interventions are required to treat severe acute kidney injuries with the high-dose methotrexate?

Kristi Posey: Emergency rescue interventions are three-fold: alkaline fluids at high rates to assist with clearance and creatinine increases, leucovorin rescue at high doses given IV, and thirdly glucarpidase rescue given at IV at a rate of 50 units/kg. However, it is really important for a few things to point out. Leucovorin alone is less affective to treat these high methotrexate concentrations as it must compete with methotrexate for cell entry. Glucarpidase provides a rapid metabolism of over 95% of the drug within 15 minutes. However, overuse of this drug then risks the patient having less exposure, lower peaks, and lower response rates. Of note, dialysis-based methods are noted to be relatively ineffective at reducing plasma methotrexate concentrations.

Kristi Posey: Now, before you give glucarpidase, you must ensure that you have access to glucarpidase. Do you have it physically at your institution? Do you share it with another institution? And if so, how long do you have to wait to have it in hand? Because the administration of glucarpidase should optimally occur within 48 to 60 hours from the start of the high-dose methotrexate infusion because life-threatening toxicities may not be preventable beyond this point.

Nancy Nix: What laboratory value is the first indication of emerging high-dose methotrexate acute kidney injury?

Kristi Posey: Consensus guidelines per Ramsay et al utilized the methotrexate level reference range for considering starting glucarpidase. The reason not to use the creatinine level alone is creatinine clearance may lag an unexpectedly high methotrexate level. However, an increase of over 50% within 24 to 36 hours of creatinine from the start does equate to a 0.99 specificity of delayed methotrexate clearance.

Kristi Posey: So this patient, upon arrival to the emergency center, is initiated on the following. She starts sodium acetate at 120 mL/hour with actually a subsequent increase to 200 mL/hour. She is initiated on leucovorin at 100 mg every 6 hours IV as well as glucarpidase at 3000 units, taking into account her weight. This is also given IV. Her hospital admission course was followed with a creatinine peak of 1.05 identified at her EC admission, and her AST and ALT remain within normal limits during her admission.

Nancy Nix: At what point was her methotrexate clearance less than 0.1?

Kristi Posey: She formally clears less than 0.1 on day 9.

Nancy Nix: Perfect, thank you. What are renal and non-renal toxicities of delayed methotrexate clearance?

Kristi Posey: So delayed methotrexate clearance creates increased exposure to the toxic concentrations of methotrexate, which cause the worsening renal function but also exacerbations of non-renal adverse events such as myelosuppression, mucositis, dermatologic toxicity, hepatotoxicity, and, as was noted here, this patient had frank altered mental status and lethargy, which was a clear substantial change from her baseline performance status. However, it is important to note that these are considered reversible injuries, and appropriate expedited treatment of the rescue drug allows for optimal clearance and resolution of these symptoms, including resolution of the creatinine to pre–methotrexate injury baseline.

Kristi Posey: This patient was discharged on day 5 at the time that we had confirmation of appropriate clearance as well as improvement of her toxicities. She had resolving oral ulcers, her creatinine level was coming down, and her methotrexate at that time of discharge was 0.14 and trending down subsequently. She formally cleared, as we previously discussed, on day 9 her appropriate outpatient monitoring at less than 0.1. With an additional five days of rest extending her cycle, her creatinine resolved to a new post–methotrexate injury baseline of 0.71. Therefore, we proved that by starting glucarpidase within 48 to 60 hours from the start of high-dose methotrexate infusion that we were able to revert potentially life-threatening toxicities. Further cycles were administered inpatient for closer monitoring but without any further delayed clearance and then planned alterations with high-dose ifosfamide were also completed.

Nancy Nix: Let us talk about our key takeaways from this discussion. Treatment protocols for high-dose methotrexate at any institution should include support strategies involving pretreatment counseling on urine testing, leucovorin doses, timely lab draws for both peak and subsequent values, alkaline IV fluid use, and warning symptoms that would result in the need for emergent rescue with glucarpidase and support. Risk factors for high-dose methotrexate–induced acute kidney injury and subsequent need for glucarpidase include baseline chronic kidney disease, extensive comorbidities, pretreatment volume depletion, both pre- and during treatment acidic urine and identifiable drug interactions. Utilizing a team approach for chemotherapy administration and subsequent monitoring for identification of patients with delayed high-dose methotrexate clearance and the need for emerging intervention is critical to timely decision making and reversibility of toxicities, morbidity, and the future use of active nephrotoxic agents in osteosarcoma. These are documented objective consensus guidelines for the use of glucarpidase; however, inappropriately high levels of methotrexate

should be correlated to clinical findings and lab abnormalities with daily review by the entire primary team for the treatment initiation and until appropriate clearance is achieved to less than 0.1 µM.

Nancy Nix: Thank you, Kristi, for joining us today, and thank you for watching this video. Please join us for the second segment in this series.