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

Case Study 2: HDMTX-Induced AKI in CNS Lymphoma

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

Haleigh Mistry: Thank you. Yes, I am Haleigh Mistry. I am one of the physician assistants at MD Anderson Cancer Center in Houston, Texas. I work in the Department of Lymphoma and Myeloma.

Nancy Nix: Thank you, Haleigh. In this activity, using the case of a 58-year-old woman with central nervous system lymphoma, we will be discussing strategies for monitoring patients treated with high-dose methotrexate for acute kidney injury, patient and disease characteristics associated with glucarpidase treatment, and how to treat patients using the best available evidence and updated guidelines.

Nancy Nix: But first, let us 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 the prolonged exposure to toxic methotrexate concentrations 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 the mortality rate of 6%. Before we jump in to the case study, Haleigh, could you take a minute and tell us a little about primary CNS lymphoma?

Haleigh Mistry: Primary CNS lymphoma is a highly aggressive non-Hodgkin lymphoma confined to the CNS, including the brain, spine, cerebrospinal fluid, and

eyes. In immunocompetent patients, it is rare and comprises about 4% of all intracranial neoplasms and 4 to 6% of all extranodal lymphomas. It typically responds to both chemo and radiation; however, it does have inferior survival outcomes compared to other lymphomas outside of the CNS. In recent years, with the introduction of high-dose methotrexate, we have seen durable responses and treatments in half of the patients, and therapy can be associated with late neurotoxicities. However, CNS lymphoma is associated with a poor prognosis for patients that have failed first-line therapy.

Nancy Nix: So, Haleigh, take us into your case study.

Haleigh Mistry: So we have a 58-year-old nondiabetic woman with a two-month history of gait imbalance and worsening one-sided weakness who presents to the clinic for diagnosis and treatment. MRI imaging reveals a homogenous gray mass. Biopsy reveals diffused large B-cell lymphoma, and neoplastic cells are CD20 positive with a Ki-67 of 75%. Upon further staging, PET-CT, MRI of the spine, and ophthalmologic consultation, and bone marrow are all negative for further involvement. Baseline labs are established, and these are within normal limits. The patient's chest x-ray is also negative for pleural effusions. The patient's current medications include pantoprazole and scopolamine eye drops. as well as dexamethasone.

Nancy Nix: Are there any contraindications for initiating high-dose methotrexate therapy?

Haleigh Mistry: Good question. Yes, so there are several different contraindications. The first contraindication I would like to discuss is the presence of third-space fluids including pleural effusions or ascites. This is because third-space fluids lead to a prolonged methotrexate plasma half-life and subsequently lead to prolonged exposure to methotrexate. This increases the risk of toxicity. It is important to have drainage of third-space fluids prior to the administration of high-dose methotrexate, as this is recommended to help prevent toxicity. In addition, we would like to obtain baseline serum creatinine levels as well as make sure that the patient has adequate hepatic

function, renal function, as well as bone marrow function. In addition, it is important to establish if the patient has impaired urinary output or not.

Nancy Nix: There are also important potential drug interactions to include, for example, the antibiotics in the sulfonamide classes, proton pump inhibitors, which I noticed your patient is on one, the nonsteroidal anti-inflammatories, penicillins, salicylate, and probenecid. These are due potentially to competing with the high-dose methotrexate for excretion via the renal tubules, and this makes the medication list reconciliation prior to intake extremely important. So, Haleigh, take us back to the case.

Haleigh Mistry: Sure. So after undergoing chemotherapy teaching and signing informed consent the patient is admitted to the hospital for the first cycle of high-dose methotrexate. In this case, we use the DeAngelis regimen including the use of rituximab, high-dose methotrexate, vincristine, and procarbazine. The procarbazine is given on cycles 1, 3 and 5. Again, baseline serum creatinine levels and creatinine clearance were established and are normal; however, the patient's glucose level was elevated secondary to the use of dexamethasone. The patient was hydrated for the first five hours, and alkalinization of the urine pH was established. After that, the patient received high-dose methotrexate at a dose of 3.5 g/m^2 over 24 hours. Leucovorin rescue was also administered.

Nancy Nix: Haleigh, how does your institution define alkalinization of the urine? What pH level?

Haleigh Mistry: Yes, a pH level greater than 7.

Nancy Nix: You mentioned that this patient underwent five hours of alkalinization of the urine prior to high-dose methotrexate. Why is that important?

Haleigh Mistry: Methotrexate is known to have increased solubility when pH increases from 5 to 7. Methotrexate and its metabolites have up to a 20-fold increase

solubility with pH when it increases from 5 to 7. Renal tubular precipitation of methotrexate and its metabolites occur when the pH is lower than 5.7. So, it is recommended to keep the urine pH greater than 7 and to maintain in its range until plasma methotrexate levels decrease or decline to less than 0.1 μM.

Haleigh Mistry: In our case, the patient received IV hydration, which is also important. Adequate hydration is an essential part of high-dose methotrexate therapy and it helps to promote diuresis and to prevent intratubular precipitation of methotrexate. Intravenous fluids of at least 2.5 to 3.5 L/m^2/day are recommended by most high-dose methotrexate regimens. This is recommended starting 4 to 12 hours prior to the high-dose methotrexate infusion.

Haleigh Mistry: And now I am going to take you back to our case study. Starting 24 hours after infusion, methotrexate serum levels are drawn. They are redrawn at 36 hours and the methotrexate serum concentration is 41 μM via chromatography. At the same time, the patient's serum creatinine rises to 3 mg/dL from a baseline of 0.8 mg/dL. This is 1.8 mg above the upper limit of normal consistent with renal dysfunction. Because the methotrexate level at 36 hours exceeded 30 μM, glucarpidase was administered at 50 units/kg via IV push over a total of 5 minutes. Repeat levels drawn at 42 hours demonstrated a serum concentration of 21 μM, which is now below 30 μM, as expected after a single dose of glucarpidase.

Nancy Nix: At this point, your patient has received high-dose methotrexate, as well as leucovorin and now glucarpidase rescue. Let’s talk a little bit about the mechanisms of action of these drugs and how they interact. Beginning with methotrexate, in 1947 Dr. Sidney Farber together with a team of researchers demonstrated the antifolate antimetabolite properties of methotrexate. It was later shown that methotrexate competitively inhibits dihydrofolate reductase with 1,000 times greater affinity. Because the folic acid cycle is essential in the biosynthesis of thymidine, purines, and pyrimidines, methotrexate interferes with the production of DNA, RNA, proteins, and thymidylates. High-dose methotrexate exceeding 500 mg/m^2 infused over 2 to 36 hours, where your patient has received

supportive care including hyperhydration with alkalinization of the urine, should then receive leucovorin rescue.

Nancy Nix: Leucovorin is also known as folinic acid and structurally as 5-formyl tetrahydrofolic acid. When administered per protocol following the initiation of high-dose methotrexate and preferably within 24 to 42 hours, cellular metabolism is restored and decreases the risk of permanent end-organ damage and potentially death, which may occur following sustained high systemic methotrexate levels. Leucovorin is dosed using standard guidelines, but when methotrexate plasma concentrations are above 5 μM, some regimens calculate the dose as the plasma methotrexate concentration multiplied by the patient's body weight in kilograms. It is important to note that while minimizing methotrexate toxicity, leucovorin does not have any action resulting in the reduction of serum methotrexate levels, and if administration of leucovorin is delayed beyond 48 hours following initiation of high-dose methotrexate, it significantly increases the risk of morbidity.

Nancy Nix: This brings us to the important role of glucarpidase. This carboxypeptidase enzyme extracellularly reduces methotrexate to glutamate and 4-deoxy-4-amino-N 10-methylpteroic acid, or DAMPA, both of which undergo hepatic metabolism, providing an alternative route of methotrexate elimination for patients with impaired renal function or who are experiencing delayed clearance, such as in the situation of third spacing as we previously discussed. Because leucovorin and glucarpidase minimize methotrexate toxicity by both intracellular and extracellular mechanisms, understanding the role of each agent is important. Without the administration of glucarpidase, continued administration of leucovorin will not change the patient's overall risk of permanent end organ damage.

Nancy Nix: Haleigh, what are potential side effects of glucarpidase about which patients should be counseled prior to administration?

Haleigh Mistry: Well, side effects of glucarpidase are rare. Some potential adverse events include paresthesia, flushing, nausea and/or vomiting, hypotension, pruritus, fever, and headache.

Nancy Nix: Is there any interaction between leucovorin and glucarpidase?

Haleigh Mistry: Yes, in fact it is contraindicated to administer glucarpidase simultaneously with leucovorin. This is because leucovorin is inactivated by glucarpidase. It is important to wait at least 2 hours after leucovorin administration prior to giving the glucarpidase. This allows for best results.

Nancy Nix: What would be the appropriate monitoring of the plasma methotrexate levels?

Haleigh Mistry: Plasma methotrexate levels are usually drawn at 24, 48, and 72 hours after starting the methotrexate infusion. However, if a patient is experiencing acute kidney injury, often times it is indicated to draw these levels at a more frequent interval. Serum methotrexate levels should be followed until the plasma level is less than 0.1 μM. Some indications for giving glucarpidase include the serum creatinine significantly elevated relative to the patient's baseline, which is indicative of high-dose methotrexate–induced acute kidney injury.

Nancy Nix: Haleigh, as you are completing periodic methotrexate serum level evaluations, are there any specific timeframes and serum levels which would indicate the need for immediate administration of glucarpidase?

Haleigh Mistry: Yes. According to consensus guidelines if methotrexate levels at 36 hours are greater than 30 μM or at 42 hours greater than 10 μM or at 48 hours greater than 5 μM, this would indicate the need for administration of glucarpidase, which should occur within 48 to 60 hours from the start of methotrexate infusion. Beyond this point, life-threatening toxicities may not be preventable.

Nancy Nix: The narrow window for administration certainly indicates the need for keeping glucarpidase on hand or having ease of access from your supplier. You should inquire at your institution if you keep glucarpidase on hand and, if not, how quickly could you obtain it, perhaps by borrowing from another institution or receiving a quicker shipment from your supplier.

Nancy Nix: In situations where a patient is not able to receive glucarpidase rescue within the 60-hour window, alternative therapy options are available, but they are not without risk. For example, studies of leucovorin therapy alone have shown that unnecessarily high doses of the rescue drug are associated with treatment failure, and that "excessive rescue" with leucovorin can interfere with the efficacy of methotrexate during the next treatment course.

Nancy Nix: Hemodialysis has also been studied and used as a treatment option for delayed high-dose methotrexate clearance. This approach is able to clear the methotrexate that is free in the plasma. However, because methotrexate has a relatively high volume of distribution, patients often experience a rebound effect of the free methotrexate once the dialysis is stopped. Dialysis clearance of methotrexate also involves multiple rounds and takes about 5.6 days or more, compared with glucarpidase therapy, which can be effective within 15 minutes of administration. Further, hemodialysis comes with its own set of risk factors, including myocardial infarction, stroke, and intradialytic hypotension—all of which supports the importance of ensuring a clear plan for access to glucarpidase for timely therapy. In fact, a recent study examined glucarpidase rescue and dialysis therapy among patients with acute kidney injury. Haleigh, can you walk us through those findings?

Haleigh Mistry: The administration of glucarpidase was associated with decreased mortality and a decrease hospital stay. In a study of Medicare patients, the average length of hospital stay in patients with CNS lymphoma who received high-dose methotrexate and had acute kidney injury that received glucarpidase was 14.7 days. However, the average length of hospital stay in patients with CNS lymphoma who received high-dose methotrexate and

had acute kidney injury but did not receive glucarpidase was much longer. Medicare patients that received glucarpidase also had a lower mortality rate, inpatient mortality rate, and a lower 90-day mortality rate than patients who did not receive glucarpidase. In another study, glucarpidase caused a clinically more important 99% or greater sustained reduction of serum methotrexate levels and provided noninvasive rescue from methotrexate toxicity in patients with renal impairment.

Haleigh Mistry: Now, to wrap up our case study. Rapid identification of high-dose methotrexate acute kidney injury allowed for administration of glucarpidase within the guideline-recommended timeframe, allowing the patient's renal function to fully recover

Nancy Nix: A couple of other points I wanted to note about glucarpidase: Leucovorin rescue should be restarted 2 hours after the administration of glucarpidase, using the methotrexate level prior to glucarpidase therapy to determine the dose. In order to keep the methotrexate from re-entering the bloodstream from the tissues, patients should then receive leucovorin for at least 48 hours after glucarpidase. Patients should then be treated with leucovorin and have their plasma methotrexate levels monitored until they reach less than or equal to 0.1 μM. And according to consensus guidelines, administering glucarpidase a second time within 48 hours of the first dose during the same methotrexate course is not recommended, as it may cause decreased efficacy of the high-dose methotrexate.

Nancy Nix: Let us discuss our key takeaways from this session. We must be aware of contraindications to high-dose methotrexate including third-space fluids, which can prolong methotrexate plasma half-life and subsequently increase exposure to methotrexate and the risk of toxicity; the presence of a serum creatinine; the use concomitantly of sulfonamides, proton pump inhibitors, nonsteroidal anti-inflammatories, salicylates, and probenecid, as these drugs compete with the high-dose methotrexate for excretion via the renal tubules. It’s also important to ensure patients have adequate hepatic, renal, and bone marrow function, as well as normal urinary output prior to initiation of methotrexate. Adequate hydration, including achieving urine alkalinization (> pH 7), leucovorin use, and glucarpidase, are all methods to reduce the instance of acute kidney injury associated

with high-dose methotrexate. To ensure appropriate and timely treatment for acute kidney injury, it is important to understand the mechanisms of action of all drugs, included in the regimen, for example, how methotrexate interferes with the production of DNA, RNA, proteins, and thymidylates; how leucovorin acts to “rescue” cells by providing reduced folate and working intracellularly to sustain the cell; and glucarpidase working extracellularly to guard the cell and help reverse high-dose methotrexate–induced acute kidney injury together. The timing of glucarpidase administration is extremely important. We must wait at least 2 hours after leucovorin administration prior to the administration of glucarpidase. Administration of glucarpidase should optimally occur within 48 to 60 hours from the start of the high-dose methotrexate infusion. Based on data from a recent study of Medicare patients, the administration of glucarpidase is associated with improved outcomes, decrease mortality, and a decreased length of hospital stay in patients with acute kidney injury following the administration of high-dose methotrexate.

Nancy Nix: Thank you so much, Haleigh, for joining me and thank you, viewers. Please be certain to view the additional segment of this two-part series. Thank you.