Clinical Updates in Acute Kidney Injury:
Outcomes for Patients Treated with High-Dose Methotrexate

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Hi. Welcome to *Clinical Updates in Acute Kidney Injury: Improving Outcomes for Patients Treated with High-Dose Methotrexate*. I am Abby Miske, a clinical pharmacist with Seattle Cancer Care Alliance specializing in adult hematology and oncology.

Although high-dose methotrexate has been used for many decades in oncologic care, it is still an important component of modern treatment in several regimens for patients with solid tumors and hematologic malignancies, including acute lymphocytic leukemia and osteosarcoma. However, delayed clearance of high-dose methotrexate, usually considered doses higher than 500 milligrams per meter squared, can lead to significant morbidity and mortality. Historically, severe toxicity occurred in approximately 10% of patients with a 6% toxic mortality rate.

More recently, the incidence of severe, life-threatening toxicity has been reduced to less than 1% by implementation of rigorous supportive care measures to prevent acute kidney injury.

In this interactive program, we will explore 2 cases of patients with acute kidney injury after receiving high-dose methotrexate. We will discuss the importance of monitoring methotrexate and serum creatinine concentrations, indications for guideline-recommended treatment of AKI caused by high-dose methotrexate, triggers for initiating treatment, concomitant leucovorin rescue, importance of administration within the treatment window, and potential immunogenicity related to guideline-recommended therapy.

Let's Meet Mr. Morris

Your patient today is Mr. Morris, a 68-year-old retired teacher who was recently diagnosed with primary CNS lymphoma. He is being admitted for his first cycle of high-dose methotrexate, rituximab, and temozolomide or MTR.

Mr. Morris has hypertension, type 2 diabetes and congestive heart failure. He is currently taking lisinopril, carvedilol, furosemide, aspirin and metformin. Mr. Morris has a baseline serum creatinine of 1.1m/dL. All of his other labs are within normal limits.

Risk Factors

What risk factors does Mr. Morris have for developing AKI secondary to high-dose methotrexate?

- Age
- Heavily pretreated
- Drug interaction – furosemide
- Dehydration
- Drug interaction – aspirin
- Low albumin
- Drug interaction – lisinopril
- Multiple comorbidities
- Elevated LDH
- Borderline baseline serum creatinine

Mr. Morris has several risk factors that increase his risk for developing acute kidney injury. Because renal function naturally decreases with age, his advanced age may be a factor to consider when weighing risk of kidney toxicity.

The use of aspirin, as well as other salicylates, probenecid, sulfisoxazole, penicillins, and non-steroidal anti-inflammatory drugs, should be avoided due to decreased renal elimination of methotrexate. The medical team should be on high alert for high-dose methotrexate drug interactions when reconciling medications on admission. For example, trimethoprim/ sulfamethoxazole may have been initiated for PCP prophylaxis as an outpatient and this agent should be held during an admission for high-dose methotrexate. High-dose vitamin C may acidify the urine and decrease renal clearance of methotrexate, and proton pump inhibitors can delay methotrexate elimination in the renal tubules, causing accumulation of methotrexate in the kidneys.

The use of furosemide has been associated with higher incidence of renal toxicity. It is unclear whether furosemide directly increases risk of renal toxicity or if it is used to mobilize fluids and maintain euvolemia correlate with populations already predisposed to significant fluid shifts. In either case, it is important to monitor fluid status very carefully and avoid both over and under hydration as third spacing and vascular depletion can put patients at higher risk of renal toxicity.

Other nephrotoxic drugs should also be avoided, including aminoglycosides, amphotericin, and vancomycin. Because lisinopril has renoprotective properties and the patient has been on this medication chronically, it does not increase our patient's risk of acute kidney injury.

Additionally, patients with baseline chronic kidney disease or multiple comorbidities are also at a higher risk of developing kidney injury with high-dose methotrexate. While his baseline serum creatinine is within institutional normal limits, it is still towards the upper end of normal. It is also important to look at serum creatinine trends over time to see if individual lab values are changed from a patient's baseline.

In addition to a borderline baseline serum creatinine, our patient also has multiple comorbidities including hypertension, type 2 diabetes and congestive heart failure, and the cumulative effect of these conditions raise his risk of renal injury. Two conditions that are contraindicated with the use of high-dose methotrexate are ascites and pleural effusion. Methotrexate tends to accumulate in the excess third-space fluid associated with ascites and pleural effusion, prolonging the patient's exposure to methotrexate and increasing risk of kidney damage. We will discuss other risk factors for acute kidney injury, including pre-treatment volume depletion and acidic urine, in a bit.

Back to Mr. Morris

Mr. Morris was administered rituximab without incident, and he isn't due to receive temozolomide until the next cycle. He was given methotrexate 8 g/m^2, which was administered over 4 hours. Leucovorin, urine alkalinization, and hydration were administered per institutional protocol.

Monitoring

What parameters are important to monitor following administration of high-dose methotrexate?

- Daily weight
- White blood count
- Urine pH
- Blood pressure
- Serum creatinine and creatinine clearance
- Fluid intake and output
- Glucose
- Methotrexate level
- LDH

Mr. Morris's 24-hour methotrexate level comes back at 40 µmol. His serum creatinine is now 1.7 mg/dL. Mr. Morris's serum creatinine has increased from his baseline since the administration of methotrexate.

What are your next steps?

- Maintain aggressive hydration and urine alkalinization
- Evaluate for third-space fluid/ascites
- Continue leucovorin
- Monitor urine output closely
- Review concurrent medications: discontinue furosemide, aspirin, and any other potential nephrotoxins
- Consider repeat methotrexate level at 36 hours

Monitoring Methotrexate Levels

After high-dose methotrexate is administered, close monitoring of serum methotrexate levels and serum creatinine is necessary. Mr. Morris received methotrexate at a dose of 8 g/m^2 over 4 hours. Because his 24-hour methotrexate level was 40 µmol/L, under the limit of 50 µmol/L for glucarpidase consideration, standard treatment with leucovorin was initiated.

At 36 hours his methotrexate level was 29 µmol/L, still under the glucarpidase treatment threshold. However, it is just barely below the threshold, and his serum creatinine has risen substantially to 2.6 mg/dL.

The decision is made to place an expedited order for glucarpidase through the manufacturer, in the event that Mr. Morris will require treatment. This product can be ordered 24/7 through the manufacturer for expedited and next-day delivery, and same-day emergency delivery is often available. Glucarpidase should be initiated within 48-60 hours of the start of the methotrexate infusion.

His 48-hour methotrexate level is above the treatment threshold of 5 µmol/L at 5.3 µmol/L and his serum creatinine continues to steadily rise. The treatment team agrees that Mr. Morris should receive a dose of glucarpidase.

Dosing Glucarpidase

Based on Mr. Morris's weight of 110 kg and the recommended dose of 50 units/kg, his recommended dose is 5,500 units. If the entire weight-based dose is not immediately available, administer the amount available. There is some data that lower doses may be effective. You should refer to your institutional dosing protocol as some institutions choose to cap the dose at a certain number of vials due to cost.

Mr. Morris's methotrexate level drops to <0.01 immediately following the glucarpidase administration, and his 72-hour methotrexate level is 0.08 µmol/L.

Would you recommend giving a second dose of glucarpidase?

- Yes
- No

Although leucovorin should be continued after glucarpidase is administered, separated by at least 2 hours, a repeat glucarpidase dose is not recommended within 48 hours due to decreased efficacy. Additionally, methotrexate levels following glucarpidase administration should be interpreted with caution for 48 hours following glucarpidase. Most clinical

laboratories measure plasma methotrexate with an immunoassay method, which cannot distinguish circulating methotrexate from the nontoxic metabolite produced by glucarpidase administration for approximately 48 hours after glucarpidase is given.

Leucovorin Administration with Glucarpidase

After the glucarpidase, you will continue treating Mr.Morris with leucovorin.

When should the next dose of leucovorin be administered in relation to the glucarpidase?

- 12 hours later
- Immediately after glucarpidase infusion
- 2-3 hours after glucarpidase infusion
- 2-3 hours after glucarpidase infusion if the methotrexate level increases above 5 µmol/L

Resolution of Case 1

Leucovorin should be continued at the dose prior to glucarpidase initiation and continued for a minimum of 48 hours post-glucarpidase AND until methotrexate returns to < 0.1. Leucovorin should be separated by 2 hours from glucarpidase administration because it may interfere with glucarpidase-mediated metabolism of methotrexate.

Mr. Morris recovered to his baseline renal function within 2 weeks and he went on to complete his high-dose methotrexate course of treatment without further renal complications.

Let's Meet Hannah

Hannah is a 16-year-old female with osteosarcoma. She is being treated with methotrexate, doxorubicin, and cisplatin, and today you are admitting her to receive her third dose of high-dose methotrexate.

Hannah was diagnosed with depression last year and was diagnosed with osteosarcoma 10 weeks ago. Recently, she has been struggling with persistent nausea and vomiting following her cisplatin chemotherapy.

Hannah is currently taking sertraline for depression. She is being treated with methotrexate, doxorubicin, and cisplatin, and is taking ondansetron and prochlorperazine as needed for nausea.

Hannah's baseline serum creatinine prior to starting chemotherapy was 0.54 mg/dL. Today, her serum creatinine was 0.8 mg/dL, potassium 3.2 mEq/L and magnesium 1.6 mg/dL. All other labs are within normal limits.

Hannah's Risk Factors

What risk factors does this patient have for developing AKI secondary to high-dose methotrexate?

- Age
- Drug interaction with sertraline
- Borderline baseline serum creatinine
- Drug interaction - sertraline
- Low albumin
- Prior chemotherapy
- Multiple comorbidities
- Dehydration
- Nausea and vomiting
- Elevated LDH

Hannah has several risk factors that put her at risk of kidney injury. Based on her serum creatinine at baseline compared with the one just prior to her third dose of high-dose methotrexate, her serum creatinine has increased almost 50%. It will need to be monitored closely.

Additionally, treatment with cisplatin has led to significant nausea and vomiting, causing volume loss and dehydration. Aggressive hydration and antiemetics will be necessary to mitigate the loss of fluids.

Supportive Care Measures

High-dose methotrexate can cause significant toxicity that may not only lead to morbidity and occasionally mortality but may also interrupt cancer treatment. To prevent toxicity, high-dose

methotrexate should be given with meticulous supportive care, aggressive monitoring, and prompt intervention.

First, it is important to discontinue or suspend medications that interfere with methotrexate clearance as we previously discussed, including aspirin, penicillin, sulfamethoxazole, probenecid, PPIs, and NSAIDs.

Hyperhydration is key and should be initiated prior to the administration of high-dose methotrexate. Urinary flow before, during, and after a high-dose methotrexate infusion should be maintained at a minimum of 2,500 milliliters per meter squared per day. If urinary flow drops below 2,000 milliliters per meter squared per day, there is a higher risk of delayed methotrexate clearance.

Another way to mitigate kidney injury is by alkalinizing the urine by giving sodium bicarbonate. Either oral or IV sodium bicarbonate can be used according to institutional standard. The purpose of alkalinization of the urine and fluid hydration is to maximize the solubility of methotrexate in the urine. For example, an increase in the urinary pH from 6 to 7 increases the solubility of methotrexate ten-fold. The urine pH should be documented to be above 7 prior to the start of a high-dose methotrexate infusion and should be maintained at this level until the plasma methotrexate concentration drops below the solubility threshold. The final supportive care measure, leucovorin, is a cornerstone of high-dose methotrexate treatment.

Which of these options is NOT a necessary supportive care measure prior to giving high-dose methotrexate?

- Maintain a urine flow of 2,500 mL/m^2 per day
- Discontinue or suspend medications that interfere with methotrexate clearance, including salicylates, sulfamethoxazole, and proton pump inhibitors
- Acidify the urine
- Administer sodium bicarbonate

Leucovorin Rescue

The final supportive care measure, leucovorin, is a cornerstone of high-dose methotrexate treatment. Leucovorin and its primary circulating metabolite prevent potentially severe and life-threatening toxicities from high-dose methotrexate by providing a source of intracellular tetrahydrofolates that enter the folate cycle downstream of dihydrofolate reductase or DHFR, which is inhibited by methotrexate. Leucovorin is particularly effective in the prevention of myelosuppression, gastrointestinal toxicity, and neurotoxicity during treatment with high-dose methotrexate. Because leucovorin effectively neutralizes the effects of methotrexate, it must not be started too early because it would then reduce not only toxicity but also anticancer efficacy.

The exact timing of leucovorin varies by treatment protocol, but in Hannah's case it should be started 24 hours after the start of the methotrexate infusion. The initial dose and frequency of leucovorin rescue depend on the specific treatment regimen and should be adjusted based on the measured methotrexate levels, as seen in the leucovorin dosing nomogram.

Serum methotrexate concentrations should be monitored with ongoing adjustments in hydration, alkalinization, and leucovorin rescue until the target of less than 0.05–0.1 μM is reached.

Back to Hannah

Hannah will receive methotrexate at 12 g/m^2 (max 20 g) over 4 hours. Leucovorin, urine alkalinization and hydration will be administered per institutional protocol.

The patient continues to struggle with nausea and vomiting after receiving high-dose methotrexate.

Her 24-hour MTX level is 52 μmol/L, SCr is 1.4 mg/dL, and her urine output has decreased.

0.8 mg/dL → 1.4 mg/dL = 75% increase over less than 48 hours, fits AKIN criteria for stage 1 acute kidney injury.

Monitor Hannah Closely

The team decides to monitor closely for now and consider glucarpidase tomorrow. The team increases hydration and optimizes antiemetics. Leucovorin and urine alkalinization are continued. Sodium bicarbonate is switched from PO to IV due to nausea. Hannah's 48-hour methotrexate level is 6 μmol/L . Her SCr is 2.8 mg/dL.

0.8mg/dL to 2.8 mg/dL = 250% increase in SCr in 48 hours

Is glucarpidase indicated?

- Yes
- No

Please select the rationale that **most closely** supports giving Hannah glucarpidase.

- Her urine output has decreased
- Her methotrexate level exceeds the maximum acceptable concentration
- Her serum creatinine has risen significantly
- A and C
- B and C

Based on both Hannah's 24-hour methotrexate level of 52 µmol/L, which is above the maximum threshold of 50 µmol/L determined by the Consensus Guidelines, AND the significant increase in her serum creatinine in such a short period of time, glucarpidase is likely indicated. The team decides to monitor closely for now and consider glucarpidase tomorrow. Hydration is increased and antiemetics are optimized, leucovorin and urine alkalinization are continued, and sodium bicarbonate is switched from PO to IV due to nausea.

Hannah's 48-hour methotrexate level is 6 µmol/L. Her serum creatinine is 2.8 mg/dL, a 250% increase in serum creatinine in just 48 hours.

Next Step in Treatment

What should be the next step in Hannah's treatment?

- Initiate dialysis
- Administer glucarpidase
- Administer another dose of leucovorin immediately followed by glucarpidase
- Continue supportive care measures and wait for next methotrexate level to be drawn

Correct! Hannah's methotrexate level of 6 µmol/L at 48 hours is above the recommended 48-hour methotrexate level of 5 µmol/L.

Guidelines published in 2018 recommend glucarpidase for a methotrexate level > 5 at 48 hours in the setting of worsening renal function. Hannah's methotrexate level of 6 at 48 hours combined with a 250% increase in serum creatinine over 48 hours, indicates that administration of glucarpidase is necessary to quickly reduce her methotrexate levels to decrease the risk of further kidney injury.

The team asks you if there is data showing a benefit for the use of glucarpidase over other interventions like dialysis. You inform them of a 2019 study of Medicare patients with methotrexate toxicity that indicated that patients who received glucarpidase had a shorter

length of stay, lower inpatient mortality and lower 90-day mortality than patients who received other interventions like dialysis instead of glucarpidase.

Timing of Glucarpidase

The team decides to give glucarpidase. You obtain authorization to order drug and are able to expedite an emergency drug delivery to arrive later that same day.

Time is of the Essence

- Ideally, glucarpidase should be administered 48-60 hours from the initiation of methotrexate infusion
- Early and rapid reduction of methotrexate concentration can lower the risk of irreversible organ damage
- According to Ramsey, et al. Consensus Guideline, life-threatening toxicities–including irreversible kidney and other organ damage that can happen if methotrexate levels remain elevated–may not be preventable beyond 48-60 hours

Monitoring and Supportive Care Post-Glucarpidase Administration

Hannah receives a dose of glucarpidase.

Ongoing monitoring and supportive care after glucarpidase administration include:

- Leucovorin should continue to be given at the pre-glucarpidase dose for a minimum of 48 hours and until MTX levels have normalized to < 0.1. Leucovorin should be administered 2 hours after glucarpidase
- MTX levels may appear falsely elevated for approximately 48 hours after glucarpidase administration if an immunoassay-based lab test is used
- Hydration and urine alkalinization should continue per standard protocol
- MTX levels should continue to be monitored daily due to potential for rebound levels following redistribution
- Renal function, urine output and daily weights should continue to be monitored closely
- Nephrotoxins should be avoided as much as possible until MTX is cleared and renal function has recovered

Resolution of Case 2

Hannah's serum creatinine continued to increase over the following few days, peaking at 6.4 mg/dL before trending back down to baseline approximately 2 weeks after receiving methotrexate. Her nausea improved, and her urine output remained stable throughout the admission.

It is possible that Hannah could be successfully treated with methotrexate again in the future.

Can Hannah receive high-dose methotrexate again?

- Rechallenge upon resolution of renal dysfunction has been done successfully in pediatric patients.
- The treatment team should consider risks and benefits to continuation of high-dose methotrexate and consider rechallenge if appropriate.
- If Hannah receives high-dose methotrexate again in the future, she should be closely monitored for early signs of acute kidney injury and glucarpidase should be accessible if needed.

Immunogenicity and Adverse Events

Despite the potential for immunogenicity related to the bacterial source of glucarpidase, hypersensitivity reactions were reported in < 1% of patients. However, 17% of patients who received 1 or 2 doses of glucarpidase developed anti-glucarpidase antibodies. The likelihood of becoming anti-glucarpidase antibody–positive was higher after repeat doses of glucarpidase, but there was no association between glucarpidase-related adverse events and presence of glucarpidase antibodies after administration.

Adverse events: Nausea/vomiting, hypotension, paresthesia, flushing, and headache (mostly grade ≤2), were recorded each in less than 3% of patients.

After recovering from this episode of AKI and optimizing her antiemetics, Hannah went on to receive high-dose methotrexate again without complication.

Important Points to Remember

- Recognize and minimize risk factors for renal toxicity in patients receiving high-dose methotrexate
- Administer appropriate supportive care for high-dose methotrexate including hydration, urine alkalinization and leucovorin rescue

- Monitor the patient closely following high-dose methotrexate administration, including daily weight, serum creatinine, fluid input and output, urine pH and methotrexate level
- Administer glucarpidase promptly within 48-60 hours if there is evidence of delayed methotrexate clearance and renal toxicity
- Continue leucovorin and other supportive care measures following glucarpidase administration

Program Conclusion

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