

# Optimizing the Treatment of Acute Kidney Injury Caused by High-Dose Methotrexate: Integrating New Guidelines to Improve Patient Care

## **Moderator:**

Zeyad Kanaan, MD  
McGovern Medical School  
University of Texas Health Science Center at Houston

## **Faculty:**

Jaya Kala, MD  
McGovern Medical School  
University of Texas Health Science Center at Houston

Heidi Trinkman, PharmD  
Cook Children's Medical Center  
Fort Worth, Texas

Zeyad Kanaan: Hello. My name is Zeyad Kanaan and I'm a medical oncologist with The University of Texas in Houston, and I'd like to welcome you to this roundtable panel discussion on *Optimizing the Treatment of Acute Kidney Injury Caused by High-Dose Methotrexate: Integrating New Guidelines to Improve Patient Care*, brought to you by the publishers of *The ASCO Post* and Harborside Medical Education. Our goals for this discussion are to give our viewers guidance in, one, optimizing the treatment of acute kidney injury caused by high-dose methotrexate, and interpreting the practical application of the *Consensus Guidelines for the Use of Glucarpidase in Patients with High-Dose Methotrexate Induced Acute Kidney Injury and Delayed Methotrexate Clearance*.

Our learning objectives for today are to identify patients treated with high-dose methotrexate who are at risk for developing acute kidney injury, and the interpretation of clinical implications of these new guidelines into the treatment of acute kidney injury in patients treated with high-dose methotrexate. Lastly, we'd like to emphasize how to plan strategies to integrate the new guidelines into practice. Here with me today to discuss this important topic are two expert panelists, Dr. Kala and Dr. Trinkman. Could you please introduce yourself?

Jaya Kala: Yeah. My name is Jaya Kala. I'm Assistant Professor at The University of Texas at the Medical Center. I'm a practicing onco-nephrologist, and I also practice at the MD Anderson Cancer Center.

Heidi Trinkman: And I'm Heidi Trinkman. I'm the clinical pharmacy specialist at Cook Children's Medical Center in Fort Worth, Texas. I specialize in pediatric hematology oncology and stem cell transplant.

Zeyad Kanaan: Thank you. Here are our financial disclosures. This activity is supported by an unrestricted educational grant by BTG International.

Now, as many of you may not have encountered some of the situations in these case studies we'll be discussing today, maybe you don't treat many conditions using high-dose methotrexate, or maybe you've just been fortunate enough not to have encountered these complications among your patients. But it's important that we bring to light this important topic, especially now that we have consensus guidelines that were recently published in *The Oncologist* in October of 2017, which aimed to help us safely administer the optimal doses of methotrexate in treating our patients. We hope to demonstrate to you through case study examples that one occurrence may alert you to be more prepared the next time you deliver high-dose methotrexate.

Zeyad Kanaan:

As you all know, methotrexate is an antifolate agent, which is by no means a new drug. It's been used for decades in treating cancers after observing that rapidly dividing cells require folic acid to support active division. Nowadays it's used in the treatment of leukemias, lymphomas, and some solid tumors, in addition to some autoimmune conditions and the prevention of graft-versus-host disease after an allogeneic stem cell transplantation. Having said that, our focus in this discussion is on high-dose methotrexate, which is often defined as greater than 500 mg/m<sup>2</sup>. We'll review three case study examples with our expert panelists here and discuss the applicability of the newly suggested guidelines in treating this condition.

Before we start, a question for you, Dr. Kala. We talked about these consensus guidelines. We mentioned high-dose methotrexate. We mentioned acute kidney injury caused by high-dose methotrexate. And shortly we're going to be talking about glucarpidase. But before we delve into all that in our first case, can you explain to us why we even need these new consensus guidelines and what need did it meet, and how does that change what we're used to doing with high-dose methotrexate?

Jaya Kala:

Sure. This set of guidelines that were recently published were by Laura Ramsey and an expert panel of people who were nephrologists and oncologists who have helped us decide and delineate as to which of the patients were actually going to benefit from the use of glucarpidase. How they have done so is by delineating which patients are the ones we should consider as considering high-dose methotrexate, depending upon the methotrexate dose, methotrexate level at different points of their treatment. That is, starting from the treatment infusion and several hours into it, what are the methotrexate concentrations and when do we decide, yes, that probably this methotrexate dose, the methotrexate level is enough to cause acute kidney injury.

For example, they do also indicate that, if you do decide to give glucarpidase, it should be within 48 to 60 hours. Why this is so is that after 60 hours, the damage is already done, so any amount of glucarpidase that you give, it would not be of any benefit to the patient. Within that time, they have divided the methotrexate dosing into three categories: If it is given less than 1 g/m<sup>2</sup> individuals, between 1 and 8 g/m<sup>2</sup>, or more than 8 g.

But what they've decided is, at 24-hour period, if they see that the methotrexate concentration in the blood is more than 120 μmol or it is more than 50 μmol in the ones who are getting the higher doses, these patients are eligible for getting glucarpidase. However, at a 36-hour period if it is more than 30, at a 42-hour period if it is than 10, and at a 48-hour period if it is more than 5, those patients will also benefit from glucarpidase. Beyond that point, even if the methotrexate concentration is high, they would not benefit from glucarpidase. However, they also do mention that all during this period the patient should be

getting the standard of care, that is leucovorin rescue. They are helping us know beforehand, before the actual toxicity appears, what is it as clinicians that we can do to help prevent acute kidney injury in these patients.

Zeyad Kanaan: Which really is very helpful, because now what I'm seeing from these consensus guidelines is it tells us what to monitor, when to monitor, when to intervene.

Jaya Kala: Correct.

Zeyad Kanaan: These are experts in the field who basically gave us these guidelines. I think what we're used to seeing is use your best clinical judgment. You mentioned glucarpidase. We'll talk about that. We'll compare that to dialysis, maybe, in one of these case studies. I guess we'll go forward from there. Thank you.

Dr. Trinkman, it would be very helpful to our viewers to understand, what is the mechanism of action of methotrexate, and then we're talking about glucarpidase as a countermeasure for methotrexate, and what's the mechanism of action for glucarpidase? Let's kind of talk about some of the mechanisms here.

Heidi Trinkman: Absolutely. That's right inside my wheelhouse, being a pharmacist. Mechanism of action of those drugs really help to understand the downstream effects of those medications. Methotrexate, it has a couple of different mechanisms, depending on the dose that the patient's receiving. The one that we're all familiar with is inhibition of dihydrofolate reductase enzyme. Basically, what that does is it keeps folic acid from being able to be reduced to folinic acid or the tetrahydrofolate, which that is a central ingredient for the cells to then go on and make the purines, which allows the cell to replicate its DNA and synthesize proteins. Without it, the cell's going to die.

Glucarpidase, how it works is it actually will cleave methotrexate through hydrolysis. This is extracellular methotrexate. It cleaves that methotrexate into two inactive metabolites. And it's rapid. It cleaves it into DAMPA and to glutamate. It's important to remember that mechanism of action of methotrexate is occurring intracellularly. The activity of glucarpidase is occurring extracellularly, to that circulating methotrexate.

Zeyad Kanaan: A direct effect against circulating methotrexate.

Heidi Trinkman: Yes.

Zeyad Kanaan: Methotrexate inhibits an enzyme. Glucarpidase will attempt to cleave methotrexate before it inhibits that enzyme on an extracellular basis.

Heidi Trinkman: Yes.

Zeyad Kanaan: Thank you. Let's go ahead and delve into our first case. Our first case is a 64-year-old female, treated for primary CNS lymphoma, with a known dose of high-dose methotrexate of 8 g/m<sup>2</sup>, infused over 4 hours, with appropriate supportive measures including urine alkalinization, including IV fluids and leucovorin. What happened next is depicted on this table. What we looked at is the methotrexate level, serum creatinine level, creatinine clearance, and urine pH. We took these measurements over three periods of time: one baseline, 24 hours, and 48

hours. Maybe we can go through these numbers and see how you would approach this scenario. We have a patient with a methotrexate level at 24 hours of 54  $\mu\text{mol/L}$ . Remember, we gave 8  $\text{g/m}^2$  over 4 hours. We have a 48-hour level of 6  $\mu\text{mol/L}$ . We saw the serum creatinine go from a baseline of 0.9 to 1.5. We saw creatinine clearance drop from 64.4 to 42.9, all in the background of a dropping urine output. Urine pH remained alkaline.

So, you've looked at the numbers. Dr. Kala, what is happening in these tubules? What's happening in the renal tubules at the moment that's causing this drop in the creatinine clearance, drop in urine output?

Jaya Kala: How methotrexate affects the kidneys is that it crystallizes in the tubules, and it causes crystallization in the tubules and not letting the tubules do their original function. They also have direct toxicity because they release oxygen free radicals, which are damaging to the kidneys and causing tubular necrosis. Those are the main effects of the methotrexate, which is running extracellularly, which is over the concentration that the kidneys can handle, and that's why they are crystallizing.

Zeyad Kanaan: That's why we see the rise in creatinine, the drop in the urine output.

Jaya Kala: That is correct. You see the rise creatinine, you see the drop in urine output. If you would see that the serum creatinine did not actually go more than 1.5 to the upper limit of his baseline. However, the urine output did go down. But we as nephrologists, we always consider "or," so it's either the creatinine going up or it's the urine output going down.

Zeyad Kanaan: Commonly what see, and sorry to interrupt you, is whenever there's any kidney insult, correct me if I'm wrong, the creatinine is not necessarily the most sensitive marker, right? The onslaught could be happening, and then a day or two later is when you start seeing a slow rise of the creatinine. Correct?

Jaya Kala: That is very correct. Because in most of our cancer patients, as you're an oncologist, you know, they are cachectic, they don't eat very well. Having less of muscle mass makes their creatinine go down anyway. If I were to rely on a marker, which is anyway going to be low in that patient, I'm going to not actually get the actual injury right away. I'm not going to pick it up. The urine output, on the other hand, is something that happens right away. You will be able to see if there is an acute kidney injury; the urine output will be the first thing that you will see go down.

Zeyad Kanaan: It's important for every patient who gets high-dose methotrexate that we do daily weights; we do I's and O's.

Jaya Kala: Correct.

Zeyad Kanaan: We basically measure all that. Thank you.

Zeyad Kanaan: Dr. Trinkman, going to back to our pharmacy question: We have methotrexate. We see methotrexate toxicity. We go by our protocols, increase leucovorin dose, increase leucovorin intensity or frequency, increase IV fluids, alkalization. How does using leucovorin compare to using glucarpidase as a rescue agent? In other words, if I'm going to give glucarpidase, why is it still important that I continue using leucovorin?

Heidi Trinkman: It's absolutely critical that you continue to use both, simply for the fact that they both work almost parallel to each other but in totally different ways. Leucovorin is working intracellularly. Leucovorin is that folinic acid or those tetrahydrofolates that we've been denying the cell access to with methotrexate. By giving them leucovorin, it's acting intracellularly to sustain the cell, allowing them to be able to make those purines, to then go on and continue their cellular processes and sustain that cell, so that hopefully you don't get cytotoxicity necessarily from the methotrexate being there. Now it's not doing anything to reduce methotrexate levels. It's not doing anything to clear methotrexate any quicker. Its main function is saving the cell that methotrexate is in. Whereas, glucarpidase is going to be extracellularly. It does not enter the cell, does nothing to get in there. What it's doing is deactivating that methotrexate that is extracellular so that it doesn't go into the cell then to create more toxicity.

Zeyad Kanaan: Really what you're saying is, if we're only using leucovorin, you're still waiting for the kidneys to clear the circulating methotrexate.

Heidi Trinkman: Absolutely. That methotrexate still has opportunity to then go into those cells and still cause toxicity.

Zeyad Kanaan: Thank you. Thank you. Great explanation. We can move on to case number two. This is a case I'm actually pretty familiar with. This is a 53-year-old male with type 2 diabetes managed with linagliptin. Hemoglobin A1C was 6.5%, morbid obesity with a BMI of 42, a BSA of 2.35. He weighs 118 kg, and he is 167 cm tall, and he's also hypertensive. He was diagnosed with B-ALL, acute lymphoblastic leukemia, and was treated on the hyper-CVAD protocol, the modified hyper-CVAD protocol. He received his induction chemotherapy with hyper-CVAD. He achieved a remission from that with some neutropenic fever complications, but fully recovered, went into a full remission, a complete remission, and was MRD-negative, in fact. Then he went on to receive high-dose methotrexate. That would be, this is a post-induction therapy now.

High-dose methotrexate on the hyper-CVAD protocol, it's 1 g/m<sup>2</sup>, and it's infused over 24 hours, so the infusion schedule is different than what you would see in primary CNS lymphoma. Then, after that, we did the protocol of leucovorin rescue, bicarbonate urine alkalinization. I was actually in contact with these providers at the time.

This is what we saw. This is what led to a discussion. The patient's baseline creatinine was 1.16. After 24 hours, which was with the first methotrexate check, the creatinine was 2.4, so a little bit over double. The methotrexate level at the time was 27.5. So at 24 hours, we have a doubling creatinine and we have a methotrexate level of 27.5. Numbers are important. At 42 hours, the creatinine continued to go up at 4.52. Methotrexate level was 6.3. For this level, glucarpidase was given. Twenty-four hours after that, the serum creatinine level was found to be 6.16, so creatinine continues to go up. But the methotrexate level went down significantly to 0.85, measured by conventional immunoassay methods, which we're going to be talking about shortly.

Zeyad Kanaan: The patient's creatinine peaked on day 10, with a level of 10.1 mg/dL. At the time, his methotrexate level was undetectable. He recovered 8 weeks later. When I say recovered, I mean the creatinine clearance was appropriate for resumption of therapy, and at the time the methotrexate level was still undetectable. This patient had a normal uric acid level. No

nephrotoxic agents were used. Supportive measures were appropriately instituted, including increasing leucovorin, intravenous fluids, and bicarbonate.

- Zeyad Kanaan: This happened actually on Easter weekend, on a Friday afternoon. Glucarpidase was not in stock. There was a discussion on how to clear methotrexate, and they talked to the patient about high-flux hemodialysis. The patient declined high-flux hemodialysis because of a bad personal history with it. He developed acute kidney injury, myelosuppression, and decreased urine output but not mucositis. Chemotherapy was resumed at the end, after he recovered. But, at the time, his leukemia actually relapsed. He was never re-treated with methotrexate because he went on to salvage therapy.
- Zeyad Kanaan: Interesting case. This is technically not as high a dose of methotrexate as you see for primary CNS lymphoma or osteosarcoma in children. This is just 1 g/m<sup>2</sup> and infused over 24 hours. Dr. Kala, could we have predicted this happening?
- Jaya Kala: We had shared this patient. I remember the phone call came on a Saturday, when I was not on call. We were trying to discuss what we were going to do on this patient when there's nothing else available. On Saturdays and Sundays, things are slow in the hospitals. Yes, of course, I think we could have predicted this happening. The reason being is he had a high BMI, so his volume of distribution of methotrexate is actually high. He has baseline chronic kidney disease from his history of hypertension and diabetes. That puts him at a risk of having methotrexate toxicity.
- Jaya Kala: Plus, as far as I remember, because I followed up on him later in the clinic, he was not a very great drinker of fluids. He oftentimes used to get dehydrated. I'm not too sure if that might have come into play, but I would give it a yes. Probably that might have been the condition too. Of course, in the hospital setting, I expect the fluids would have been given to him. Leucovorin would have been given to him. I do say yes. I may have predicted this might be a possibility for him.
- Zeyad Kanaan: A possibility, and probably a more likelihood than for another patient.
- Jaya Kala: Yes.
- Zeyad Kanaan: But would you say it would have been a high possibility to a point where I wouldn't administer methotrexate to him?
- Jaya Kala: No. It would be a high possibility just because it is this patient; another patient who had had a better BMI, a thinner individual, who did not have chronic kidney disease in the past, so not prone to having acute kidney injury, might have done better with this dose.
- Zeyad Kanaan: I think what you're saying is, if we had five patients on the ward that day who were getting high-dose methotrexate, you would have pointed out this patient as having a higher likelihood of developing this.
- Jaya Kala: Correct.
- Zeyad Kanaan: Would you have done anything different with the supportive measures? Leucovorin, intravenous fluids, alkalinization?

Jaya Kala: Alkalinization, of course. It was already done. It's just that every patient is different. How every patient reacts to any medication is very different. Everybody's cancer is different. It's very difficult to say whether I would have done anything else, because we did everything that is standard of care. There are obviously these outliers and there are some patients who would not actually fit into that and would surprise us. He was a surprise on Easter.

Zeyad Kanaan: On an Easter weekend. Of course. Thank you. That was very helpful.

Zeyad Kanaan: Dr. Trinkman, a question for you. You looked at the table. You saw that, after we gave glucarpidase, we measured the methotrexate level 24 hours later. We'll talk about intervals in a little bit. It went down by anywhere between 85% and 90%, but he had a persistent level of 0.85 [g/m<sup>2</sup>]. This is in the setting of someone who's having a drop in creatinine clearance, a drop in urine output, and a rise in creatinine. We measured it by immunoassay methods, and it was 0.85 [g/m<sup>2</sup>]. Would you have considered a second dose of glucarpidase to make it go down to an undetectable level, or what would your approach be in this situation?

Heidi Trinkman: First off, I would say no. I would not have considered a second dose, and for a couple of reasons. The first reason being that, you said yourself, we measured it with an immunoassay. The immunoassay measurement for methotrexate, within 48 hours of a dose of glucarpidase, can be erroneously elevated because it's picking up DAMPA—one of those inactive metabolites of methotrexate that glucarpidase cleaves. It's picking that up and reading it as methotrexate. Because of that, within 48 hours, if you're measuring the methotrexate level via an immunoassay, then those levels can tend to be a little bit elevated from what the actual level would be. You can measure that through HPLC [high-performance liquid chromatography], which does not pick up DAMPA as part of that methotrexate level. The problem with that is not every institution has that available—

Zeyad Kanaan: And I'm sorry, but that's liquid chromatography, right?

Heidi Trinkman: Yes. Not every institution has that. And if you are able to do that, you have to send it out. You don't get that information back as timely. It's more costly to be able to do that. There are reasons to do it and not to do it. I think we're less than 1 [g/m<sup>2</sup>], which is a good indicator. We're down to where leucovorin can handle the toxicity.

Heidi Trinkman: The other thing is glucarpidase is expensive. You really aren't getting the bang for your buck that you really need to be getting. The best efficacy from glucarpidase comes when the level is high, and so that extracellular methotrexate is there. If our level is less than 1 [g/m<sup>2</sup>], it's not necessarily indicated.

Zeyad Kanaan: Good. This was appropriately monitored.

Heidi Trinkman: Absolutely.

Zeyad Kanaan: Thank you. Back to you, Dr. Kala. What you saw here was a patient who suffered an acute kidney injury from high-dose methotrexate. You saw a declined urine output, declined creatinine clearance, and a slow rise in creatinine over a long period of time, peak at 10 days, and then a slow drop in creatinine to a normalization or back to his baseline. That took about 8 weeks. Is that what you would have expected as far as the recovery time?

- Jaya Kala: Yes. There are data out there that says, even after you have given the glucarpidase, creatinine could continue to rise for up to 3 days after that. In almost 60% of patients who have received glucarpidase, it takes about, on average, 12 to 12.5 days for the level of creatinine to come back to baseline. This is not unusual. As long as he was making urine and he had no issues with potassium being high or high calcium levels being too low or his having acidosis, my indication of acute kidney injury and his needing dialysis would depend on these factors. If that doesn't come up, I would not be in an urgent need of eliminating toxins. I would not subject him to even dialysis at that point.
- Zeyad Kanaan: Good. This is not out of the norm, completely out of the norm. As you saw, as well, dialysis was discussed, high-flux dialysis. If glucarpidase is not in stock, let's say not available, and you may want to discuss dialysis. How would you compare the two methods of elimination as far as efficacy, logistics?
- Jaya Kala: That's very surprising. I'm a nephrologist, but I'm going to say a lot of things that I don't like for hemodialysis, because it's not a benign procedure. It is something that is invasive. If you are actually subjecting your patient to hemodialysis, you ought to be very sure this patient is actually going to benefit from it.
- Jaya Kala: Some downsides to that is that with hemodialysis, when you do it for methotrexate elimination, there is a rebound effect of methotrexate that can happen once you stop the hemodialysis. The reason why this happens is because the huge volume of distribution that it has. Once you stop the hemodialysis, the methotrexate is going to come right back into circulation, and it will be ready to attack the kidneys. Basically, the patient is again prone to having acute kidney injury after that hemodialysis session.
- Zeyad Kanaan: So you continue hemodialysis?
- Jaya Kala: You cannot have 24-hour hemodialysis. We have modalities called continuous renal replacement therapy, but they're not efficient enough to remove toxins. They're very slow flow rates in which the only way you can use it is in an ICU setting in a patient who has low blood pressure, but it is not efficient enough in removing toxins, so it would not have been done and it is not high-flux.
- Zeyad Kanaan: But what I meant to say is that it can't be just one dialysis session.
- Jaya Kala: Yes. He would need multiple sessions, and in between sessions he could rebound enough to cause more kidney injury. Other than that, also, hemodialysis elimination of methotrexate, it takes about 5.6 days or so. Whereas, in comparison to that, within 15 minutes, glucarpidase can bring down the methotrexate level to an undetectable level. The disadvantage is using a procedure that might actually continue to subject a patient to a high dose of methotrexate in comparison to something that is faster-acting. Something you will always think that is why would I not do something that is quicker for my patient?
- Jaya Kala: Other than this, hemodialysis patients actually are subjected to several risk factors. They are prone to having myocardial infarction, stroke, and hypertensive episodes during that hemodialysis session. Even if a patient, such as ours, had been subjected to hemodialysis, I cannot be certain that I might not make him prone to having more acute kidney injury, with further damage to his kidneys, and actually destine him to dialysis long term. He would be



prone to having things called intradialytic hypotensive episodes. That is why we don't consider hemodialysis as a very benign procedure.

- Jaya Kala: Recently, too, we received some data from Medicare claims. We used ICD code 10 to go back in years 2013 to 2016. We went through data to see whether glucarpidase in comparison to hemodialysis or leucovorin was different for patients in terms of length of hospital stay and length of ICU stay.
- Zeyad Kanaan: That's interesting.
- Jaya Kala: And even for mortality. We did find there was a significant difference: patients who had been on glucarpidase had a shorter length of stay, a shorter ICU stay, and lower mortality risks in comparison to the ones who did not receive glucarpidase and received either just leucovorin or dialysis. There are data enough, but it is not yet published. We have a poster presentation that we will be discussing and later publishing. But this is evidence enough to show that going to the modality of hemodialysis might not always be a good option. You have to weigh the risk versus benefits before you actually offer it to your patient.
- Zeyad Kanaan: Great. Efficacy-wise, glucarpidase within 15 minutes or so, it drops your level to below toxic levels.
- Jaya Kala: Correct.
- Zeyad Kanaan: Dialysis, we're talking about frequent dialysis.
- Jaya Kala: Frequent dialysis and longer duration.
- Zeyad Kanaan: Longer duration. That affects the length of stay.
- Jaya Kala: Indeed.
- Zeyad Kanaan: I guess we'll wait to see what the cost outcomes are.
- Jaya Kala: Especially if our patients are getting sick, they have to actually go down to the ICU. They're in an ICU receiving hemodialysis. I looked up the cost of an ICU stay. The ICU hospital bed itself is about \$4,000. To add to that, if you're putting the patient through hemodialysis, you're adding the physician cost and the cost of all the other individuals who are involved in the care of the patient.
- Zeyad Kanaan: The catheter.
- Jaya Kala: The catheter, bleeding risk from that. It all adds up to a good amount, which would be billed to the patient. I do agree, glucarpidase is expensive, but we always have to see this part of it to which is not actually accounted for, all these other modalities that we're using for these patients.
- Zeyad Kanaan: Interesting. Dr. Trinkman, back to you. As part of our supportive measures, we increase intravenous fluids. Hypothetically speaking, this patient developed bilateral pleural effusions or any serosal effusion or fluid pocket. We know from understanding the pharmacokinetics of

methotrexate that it can sneak into those pockets and achieve steady state with the intravascular concentrations, and that would lead to a longer half-life and persistent levels. Let's say you had that. I think common practice right now is to drain the fluid, thoracentesis, paracentesis. Would we stick with that approach, or would we turn to glucarpidase for a persistent methotrexate level?

Heidi Trinkman: I would definitely stick with a thoracentesis, simply for the fact that it's removing the offending agent immediately, whereas glucarpidase, it's not going to get into that fluid. It's going to stay extracellular in the circulation. All you're doing is getting that small amount of methotrexate that's being released from that fluid. Yes, your glucarpidase will absolutely hydrolyze that, but you're missing what's then going to be released. Glucarpidase doesn't stay around long enough to continue to get that small amount that's being released, and so what that's doing is it's just exposing the patient to longer durations of methotrexate in the circulation. Absolutely removing the fluid removes the methotrexate as well.

Zeyad Kanaan: I believe that's what most people still do. I don't know what different institutions, as far as policies go, have. But we do chest X-rays, for instance, before any high-dose methotrexate to make sure they don't have any fluid pockets. We do our physical exam geared towards looking for ascites or any pockets of fluid. Those patients, sometimes even on an outpatient basis, get that drained before they're admitted for their high-dose methotrexate if that's possible. Really, from clinical grounds, I think it would still make sense to drain the fluids just to make the patients feel better.

Zeyad Kanaan: We can move on to our third and last case. This is a 5-year-old boy with high-risk acute lymphoblastic leukemia. I think when I said 5-year-old boy you guys expected me to say osteosarcoma, with 12 g/m<sup>2</sup> of methotrexate. But this is a boy with ALL who was treated with induction therapy with doxorubicin, vincristine, prednisone, L-asparaginase induction therapy and achieved a complete remission. Went on to receive post-induction therapy with high-dose methotrexate with the hydration, alkalinization, leucovorin rescue. We have 48-hour data to look at here.

Zeyad Kanaan: Baseline methotrexate, obviously not done baseline. But at 48 hours it was 18. You have a methotrexate level at 48 hours of 18 μmol/L. Serum creatinine went up from 0.4 to 1.1 and the creatinine clearance went down from 125 to 42 at 48 hours. First question, would you give glucarpidase in this scenario, Dr. Kala?

Jaya Kala: Definitely, because at 48 hours it is more than 5, the methotrexate concentration is there. It is high, so definitely this patient would benefit from glucarpidase.

Zeyad Kanaan: Do you agree, Dr. Trinkman?

Heidi Trinkman: Absolutely. As well, the creatinine has almost tripled. That right there is two huge red flags, and I would absolutely give glucarpidase.

Zeyad Kanaan: That's exactly what took place here. Dr. Kala, I think what we heard you say is that glucarpidase is indicated for this boy with ALL who had this toxicity. Let's assume hypothetically—we measure the methotrexate level, we measure the serum creatinine, we measure the creatinine clearance. Most of our guidelines put all of those measures into perspective as to when to decide when to give glucarpidase. But let's say you only have one

abnormal value out of these, so a suboptimal methotrexate clearance or a rising creatinine in the setting of high-dose methotrexate. Is this an "and" or an "or" decision?

- Jaya Kala: It's an "or" decision. Either you have high methotrexate concentration in the serum or you have creatinine, which is more than 1.5 off the patient's baseline. It can be either of these indications, which would prompt you to give the patient glucarpidase.
- Zeyad Kanaan: If you have a high methotrexate level, you're not really seeing much of the kidney injury yet, that is still an indication to give the rescue drug.
- Jaya Kala: Yes. The reason being is that you can start seeing the methotrexate level being high before the actual kidney injury occurs. That is why they have this indication as an "or," because you might see the methotrexate concentration level go up before the actual kidney injury's happening. It might be happening after a couple of hours when the lab tests might have not yet come back. But you can actually save time by giving the medication at the time when the patient would benefit from it most.
- Zeyad Kanaan: It's just a matter of time before we see the creatinine rise.
- Jaya Kala: Correct.
- Zeyad Kanaan: Or creatinine clearance drop. Basically, any delay—here, delay is nephrons or tubules—
- Jaya Kala: Correct.
- Zeyad Kanaan: —you said tubules, right?
- Jaya Kala: Tubules.
- Zeyad Kanaan: The delay is tubules, just like...okay. Now, at the beginning of this discussion, when we were going over the overview for the consensus guidelines and why it was put together and how it was put together, you gave us that 60-hour number. 60 hours is between 2 and 3 days. Just to help me understand, after 60 hours, if I have an indication for glucarpidase, this is a 5-year-old boy who, at 72 hours, had a persistent level. Would you give glucarpidase then, or are you saying that 60 hours is a hard cutoff?
- Jaya Kala: The guidelines that were given out was by an expert panel of individuals who are nephrologists and oncologists. They had data from several years from all the publications that have been done thus far about glucarpidase, about high-dose methotrexate. It is their opinion, their expert opinion, that this is the time when glucarpidase would be most beneficial to the patient. After 60 hours, even if one gives glucarpidase, it is very likely that the life-threatening complications have already set in. They don't say do not give it, but that is what their suggestion is, that it's best beneficial to the patient to avoid any of these life-threatening complications if it is given within 48 to 60 hours.
- Jaya Kala: Of course, these guidelines are to help guide us. This is giving us guidance in the majority of the population. But if you do see a patient who's got a higher dose of methotrexate, serum level is really high, and the patient is probably not even able to get hemodialysis, I don't see a reason why one would not be able to give it. It's a patient/physician decision, a

patient/oncologist decision. Their personal opinion that at that time would decide if they can give glucarpidase or not.

Zeyad Kanaan: I think the biggest challenges here, and I'm sorry if I interrupted you, but I think the biggest challenges with all of the data we have for this specific condition is that it's all anecdotal.

Jaya Kala: Correct.

Zeyad Kanaan: We have two different types of populations. We have pediatrics, who we know are very resilient. They recover. We have older patients who may not do as well. A lot of what we do—I'm an adult oncologist—a lot of what we do is extrapolate from pediatric data.

Jaya Kala: That is correct.

Zeyad Kanaan: I don't know that that's fair, but we don't have enough cases to do a prospective randomized controlled study using glucarpidase versus something else, unless it's maybe a national registry for this or an international trial just to collect enough patient samples.

Jaya Kala: That is right, because all the information that I had given about the Medicare claims data that we have is a retrospective study relying on the ICD codes that was given by the physician. In my experience, I've also noticed whenever the ICD codes are put in while billing is done, it oftentimes says there's acute kidney injury but it would never claim as acute kidney injury secondary to methotrexate. You're actually losing a count on that patient. Whatever information we have is actually limited because of the way it has been coded. What is needed, of course, is a prospective study in which you'll be able to compare this drug versus leucovorin versus dialysis. It can be only done when everybody's educated that you have to put that as the diagnosis.

Zeyad Kanaan: I think that was really highlighted because I said it was unfair to take pediatric data and apply it. Pediatric data—I want to say the majority of it was osteosarcoma patients who received 12 g/m<sup>2</sup>. Most of the adult data come from primary CNS lymphoma, and that's 8 g/m<sup>2</sup>, but yet you see more methotrexate toxicity and actually a suggestion, I don't think that it was statistically significant, but I think there was a suggestion to increased mortality rates secondary to methotrexate toxicity in older patients, although we're using a lower dose than what we do in pediatrics. It just kind of tells you that we might not really be able to extrapolate exactly what happens with your pediatric patients to our adult patients.

Jaya Kala: That is correct.

Zeyad Kanaan: Any thoughts, Dr. Trinkman?

Heidi Trinkman: No. I think all of that is pretty much what we see. Even with pediatric patients, if it gets to that 72-hour level and that's when we start to see the red flag of increased creatinine or an elevated level that's the slope of their clearance isn't cooperating with us, if there's enough, if the level is high enough, I still think that we would potentially take that into consideration as a clinical judgment call to administer the dose of glucarpidase.

Zeyad Kanaan: Guidelines are guidelines.

Jaya Kala: Correct.

Zeyad Kanaan: They're there to help you. They don't eliminate your clinical judgment.

Jaya Kala: That is correct.

Heidi Trinkman: It's more than we had before.

Zeyad Kanaan: More than we had before.

Heidi Trinkman: That's right.

Zeyad Kanaan: Thank you. I think we talked about this a little bit, but I think it's really important to emphasize this. We talk about scientific approaches, biochemical approaches. We talked about pharmacokinetics, pharmacodynamics. But just realistically—first of all, do any of you sit on their P&T committee? The pharmacy and therapeutics committee?

Jaya Kala: Not me.

Zeyad Kanaan: Dr. Trinkman?

Heidi Trinkman: At our hospital, actually, my role is, if there is a medication that's coming for consideration to P&T, if it has to do with oncology, then they would call me in to interpret the information and to help guide the decisions when they do consider the drug for a patient.

Zeyad Kanaan: You have involvement. I think you're aware of what the committee does, at least, right?

Heidi Trinkman: Right.

Zeyad Kanaan: From a strategy standpoint, we talked about our case number two, which was the patient with the methotrexate toxicity that happened on Easter weekend. Glucarpidase not in stock, so we had to go for discussions on hemodialysis. What are the barriers to have glucarpidase in stock for when we need it emergently like this?

Heidi Trinkman: Cost.

Zeyad Kanaan: It's really cost, isn't it?

Heidi Trinkman: There is cost. I think it's difficult to convince the administration that, to have something that is that much money sitting on your shelf for the occasion that you might need it. But I will say that convincing arguments do come when you present patient information and you present patient scenarios that have happened, just like the one that you had. Because, yes, it is true that you can get next-day delivery in most cases, but the problem comes when it is Friday night or it is an Easter weekend, and you have that patient that you've identified needs this drug, that needs this. I always tell my physicians, time is toxicity. We need to act as soon as we know. It becomes that wait until you can get it because you don't have it on your shelf is excruciating for us, knowing—

Zeyad Kanaan: What if it's a regional supply? What if you're in a medical center that has three or four hospitals, and one hospital has it, but you need it and you borrow? Is that something you feel that's feasible?

Heidi Trinkman: I tell people, find out who has it and make friends with them. Because if you're not allowed to keep it, know who in your area does have it.

Jaya Kala: I remember that time, we were trying to see if any other hospital had it. We were for sure certain that there was one hospital which was close by had it, but would refuse to give it because, if they unstock it, there's no more way of getting it. They need it during their time. We didn't have an ability to get it from another hospital. Of course, maybe we should have made them friends. We should have done more before.

Zeyad Kanaan: Being from Houston, at times of Harvey, storms like that, where are you going to get it at that time?

Jaya Kala: True. True.

Heidi Trinkman: Having a game plan. If your administration will not allow you to stock it, it's important that you have that game plan for the "what if." What if you have a hurricane?

Jaya Kala: True.

Heidi Trinkman: What if it is an Easter weekend? What are you going to do?

Zeyad Kanaan: We're really not talking about a very common scenario. Harvey is not a common scenario either. But really, all it takes is that one patient that will make you want to go and look for your contingent plan, or really to preplan to have those emergent situations or emergent rescue medications available.

Jaya Kala: Agreed.

Zeyad Kanaan: Then, when you do try to give a drug like that, I think this kind of goes across the board in the nation, you run into many obstacles, that being the many phone calls you have to make to actually get the drug, and then you have looking at it in the stock, and then you talk about cost, and then you get suggestions saying, "Well, why don't you just increase leucovorin a little bit more? Why don't you wait another 24 hours and see? Maybe the methotrexate level goes down." Any thoughts? Is that something that you see as well?

Jaya Kala: I believe it's just a matter of being able to educate those people who are right in front of us, to be able to tell them exactly how it works, because if they understand the fact that leucovorin is working intracellularly but the methotrexate is still out there which is causing acute kidney injury, what I would of course tell them is that, "Are you ready to spend all this money on the hemodialysis that this patient is going to undergo, actually subject him to the risk of continuously being on hemodialysis and not even sure that that session of hemodialysis will take out that level of methotrexate?" That is an ongoing process. It has to be broken down to, how much am I going to spend on that vial of glucarpidase in comparison to how much I'm going to spend on that patient during that hospital stay, including the ICU, including the hemodialysis?

Jaya Kala: We're actually trying to see a one-to-one comparison, but it is very, very difficult to come up with that. That is the only way one can compare and see. It's a life of a patient we're talking about. Hemodialysis is not just that I can just dialyze somebody. I have to be very cognizant of the fact that this patient is already undergoing chemotherapy for a cancer which is a difficult diagnosis anyway. Our patient refused hemodialysis. He had a reason to refuse, because his family member did not do too well on hemodialysis. That stigma stays on that patient. "I'm on hemodialysis. This is the end of the world for me." We have to be very cognizant of what our patient is going through and decide therapy according to it.

Zeyad Kanaan: I remember the case when—atypical HUS [hemolytic uremic syndrome] is now treated with a drug called eculizumab.

Jaya Kala: Correct.

Zeyad Kanaan: Which is also a very expensive drug. But what we used to do is long-term hemodialysis. Some of the arguments then were, why don't you use eculizumab? Hopefully you'll get to a point where there is an actual stop date for it. Maybe. Maybe not. But then that might actually be cheaper to use than pretty much lifelong dialysis because they're always kind of at risk of developing—maybe lifelong, but long-term for sure, dialysis.

Jaya Kala: Correct.

Zeyad Kanaan: Eculizumab now is pretty much widely used for the condition.

Jaya Kala: True.

Zeyad Kanaan: Now the million-dollar question. You have a patient that went through all this trauma. You increased supportive measures. You called your onco-nephrologist. You call your pharmacist. You call the hospital administration to get the drug. The drug was emergently delivered to you within 24 hours. Now the patient recovered and now they're due for their next high-dose methotrexate. Primary CNS lymphoma patients, they get high-dose methotrexate every 2 weeks for let's say a year. Would you retreat them with high-dose methotrexate at this point?

Jaya Kala: I would, because there is data out there which was published by the St. Jude Children's Hospital. They had rechallenged about 13 patients, out of which 11 did really well. This data has not been replicated in adults as yet, but I don't see a reason why one would not do it, because if that is their treatment that they have to get, I would not hold them and say, "You cannot get your methotrexate which is probably lifesaving for you."

Zeyad Kanaan: But you'll need to get your contingency plan in order, too, right?

Jaya Kala: Yes. Of course.

Zeyad Kanaan: What do you think, Dr. Trinkman?

Heidi Trinkman: I know I agree with that. That information is very compelling. I know that in pediatrics we tend to not adjust their next course based off of previous delayed clearance. It does feel like, from our experience, we've had quite a few patients who have had a renal injury and require

glucarpidase go on to then have perfectly fine administrations of subsequent cycles and not require any kind of an additional dose reduction or adjustment in therapy.

Zeyad Kanaan: It's actually very interesting that you say that. For primary CNS lymphoma, we have the best outcomes for the patients who receive the optimal dose of methotrexate. But what you commonly see is, if someone's struggled with methotrexate the first time around or after the second time or third time, the one after that, some oncologists, and I know this for a fact, would say, "You know what? Let's not use 8 g/m<sup>2</sup>. This patient struggled before. Let's cut it to 4 g/m<sup>2</sup>." That's very common to happen. But we know, all of us know, that the response is dose-dependent. It's CNS lymphoma. You have to get that high level to reach the CNS, and the response is dose-dependent. With rechallenging, I think if you have a mechanism like glucarpidase or any mechanism to get rid of circulating methotrexate, which really at this time is only glucarpidase, efficiently, as Dr. Kala already explained, that will allow us to continue to give the optimal dose for these patients.

Zeyad Kanaan: Some of them get into this remission, and then after that they decide to cut the dose based on the same argument. But that's probably not optimal. For some diseases like primary CNS lymphoma, I don't really know that there is an alternative to high-dose methotrexate. I probably don't have an option to switch therapy. ALL, maybe. But for primary CNS lymphoma, I think that will be a big challenge.

Jaya Kala: True. In that case, I would just add to that, even if you have to give it and the patient does develop acute kidney injury, the patient is more likely to die of the CNS lymphoma rather than the acute kidney injury. One always has to weigh the risk versus benefits and just go ahead and do it.

Zeyad Kanaan: Absolutely.

Thank you, Dr. Trinkman and Dr. Kala for joining us today for this educational session.

Jaya Kala: Thank you for having us.

Heidi Trinkman: Thank you.

Zeyad Kanaan: We hope you enjoyed this discussion on *Optimizing the Treatment of Acute Kidney Injury Caused by High-Dose Methotrexate: Integrating New Guidelines to Improve Patient Care*, brought to you by the publishers of *The ASCO Post* and Harborside Medical Education. I would also like to thank our panelists again, Dr. Kala and Dr. Trinkman, for their valuable insights. For more information, please visit [ASCOPost.com](http://ASCOPost.com).

**Link to: Consensus Guideline for Use of Glucarpidase in Patients with High-Dose Methotrexate Induced Acute Kidney Injury and Delayed Methotrexate Clearance**

<http://theoncologist.alphamedpress.org/content/early/2017/10/27/theoncologist.2017-0243.short>