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https://reachmd.com/programs/cme/oncology-emergency-essentials-addressing-tumor-lysis-syndrome-in-your-practice/9814/

Released: 10/27/2017
Valid until: 10/27/2018

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Oncology Emergency Essentials: Addressing Tumor Lysis Syndrome in Your Practice

Narrator:
Welcome to CME on ReachMD. This activity titled *Oncology Emergency Essentials: Addressing Tumor Lysis Syndrome in Your Practice* is developed by Clinical and Patient Educators' Association and CME Solutions International and supported by an educational grant from Sanofi US. The expert guest for this activity is Dr. Mitchell Cairo, Chief of Pediatric Hematology, Oncology and Stem Cell Transplantation and Director of the Children and Adolescent Cancer and Blood Disease Center at Westchester Medical Center, as well as Associate Chair and Professor of Pediatrics at New York Medical College. Prior to beginning this activity, please be sure to review the faculty and commercial support disclosure statements as well as the learning objectives. Here is your host, Dr. Prathima Setty.

Dr. Setty:
We're going to discuss tumor lysis syndrome, one of the most common and potentially fatal oncologic emergencies encountered in clinical practice, including strategies to assist you identify and manage these patients. Dr. Cairo, welcome to our program.

Dr. Cairo:
Well, it's a pleasure to be here. Thank you.

Dr. Setty:
Dr. Cairo, can you describe to us what exactly tumor lysis syndrome is?

Dr. Cairo:
Tumor lysis syndrome results from the rapid destruction of cancer cells, and represents a group of metabolic abnormalities that result from this destruction. During the process of destroying these cancer cells, they release their intracellular contents into the bloodstream, which includes the release of nucleic acids, phosphorus, potassium and other proteins. The results of this release can lead to increases in uric acid known as hyperuricemia, increases in phosphate known as hyperphosphatemia, increases in potassium known as hyperkalemia or secondarily lead to decreases in the calcium known as hypocalcemia. They may occur spontaneously, but more often they occur in response to the treatment of the underlying cancer.

Dr. Setty:
Now, what are some of the consequences that can result from these metabolic abnormalities?

Dr. Cairo:
Well, tumor lysis syndrome is a life-threatening complication, and some of the systemic complications occur include the kidney, in particular, leading to acute kidney injury or AKI. It can lead to cardiac arrhythmias or dysrhythmias and potentially result in sudden cardiac failure. There are neurological changes such as seizures, somnolence and others, and, in the worst case scenario, can result in death. Specifically, high levels of uric acid, as known as hyperuricemia, can lead to precipitation of the uric acid in the renal tubules, and this leads to the acute kidney injury I mentioned earlier. High levels of the phosphorus, known as hyperphosphatemia, can lead to precipitation of calcium phosphate crystals also in the renal tubulars, and this can lead to acute kidney injury and also lead to secondary hypocalcemia, which can further act and exacerbate the hyperphosphatemia, further exacerbating the acute kidney injury, and, of course, high levels of potassium, otherwise known as hyperkalemia, can lead to cardiac irregularities and dysrhythmias and also have neuromuscular effects. Patients who also have concomitant acute kidney injury can also exacerbate hyperkalemia. These effects tend

to occur within 12 to 72 hours after initiation of cancer treatment, most commonly after cytotoxic chemotherapy, and these complications can also lead to a compromise of the efficacy or the delay in the administration of further chemotherapy. It's paramount that prompt recognition is utilized in diagnosing or preventing TLS followed by aggressive management.

Dr. Setty:
Dr. Cairo, how are TLS symptoms recognized and diagnosed?

Dr. Cairo:
Well, Dr. Michael Bishop and I developed a classification definition and grading system in 2004 that we published that had been modified from a previous classification by Hande & Garrow in 1993. And we divided the definitions in tumor lysis syndrome into both laboratory tumor lysis syndrome and clinical tumor lysis syndrome. In the category of laboratory tumor lysis syndrome, the definition requires the presence of 2 or more abnormalities in the following laboratory values: increase in uric acid, increase in potassium, increase in phosphorus and/or a decrease in calcium, either an absolute increase or at least a 25% increase from the patient's baseline value, usually occurring approximately 3 days before or 7 days after the initiation of chemotherapy.

Now, the diagnosis of clinical tumor lysis syndrome requires first the presence of laboratory tumor lysis in addition to one or more of the following clinical complications: acute kidney injury, cardiac dysrhythmia, sudden death and/or seizures.

Dr. Setty:
So, Dr. Cairo, in which malignancies is TLS most commonly diagnosed?

Dr. Cairo:
Well, a concurrent wide variety of malignancies. However, it more commonly occurs in a subset of hematological malignancies where there is both a high tumor volume and also a high proliferative rate or one or the other, such as Burkitt's lymphoma, B-cell acute lymphoblastic leukemia and some forms of B-cell lymphomas. You'll see much less frequently in hematologic malignancies or solid tumors that have slower proliferative rates, or growth rates, such as multiple myeloma, Hodgkin's lymphoma, etc. However, the incidence of tumor lysis syndrome has been increasingly reported in malignancies not usually considered at high risk due to more effective cancer treatments.

Dr. Setty:
Can you provide some examples of newer cancer therapies that have been reported to cause TLS?

Dr. Cairo:
Yeah. So, for example, venetoclax, which is an inhibitor of bcl-2, a small molecule inhibitor, has been recently noted to cause a 5% to 10% incidence of TLS in patients with chronic lymphocytic leukemia. Alvocidib, a cyclin-dependent kinase inhibitor, which is used with cytarabine and mitoxantrone in patients with acute myeloid leukemia, has been reported to have a high incidence of TLS upwards to 45% in that group. The proteasome inhibitors, bortezomib and carfilzomib, have also been reported to cause TLS, particularly in patients with multiple myeloma, which historically, as I said earlier, TLS had been reported to be usually rare in that subgroup of patients. Clinicians, however, should be alerted for TLS even in patients with lowest disease who have high disease burdens and/or who are treated with new or more effective agents that result in a rapid onset of tumor cell lysis.

Dr. Setty:
So how can clinicians identify patients at risk for TLS?

Dr. Cairo:
Well, as I discussed earlier, there are tumor-related factors that we know are associated with an increase in TLS. As I mentioned, high tumor cell proliferation rates, large tumor burdens, which also may be reflected in bulky disease, patients with high levels of lactate dehydrogenase or LDH levels as reflective of high tumor burdens, and obviously, as we discussed earlier, tumors that are highly sensitive to chemotherapy. There are also patient-related factors that may dispose patients to TLS that are not as much tumor related, and those include patients with preexisting renal dysfunction or maybe even renal involvement, as well as patients' older age. These also seem to be risk factors for patients developing TLS.

Dr. Setty:
That's good information, Dr. Cairo. Now, can you give us a specific example of a patient that was at risk for TLS in your practice to help demonstrate the steps you took to identify this risk? Also, were any interventions needed once a risk for TLS was identified?

Dr. Cairo:
So, one case comes to mind would be a 55-year-old gentleman, who was diagnosed with stage 4 diffuse large B-cell lymphoma, some marrow involvement and also had presence of large bulky disease. His original blood work was reflected with a white count of 10,500,

but a very high LDH level of 1900, but a uric acid level of 6 and potassium at 4.5, phosphate of 5.6, but also was predisposed to having preexisting renal dysfunction with a BUN of 40 and creatinine of 2.1. This gentleman was treated with standard doses of rituximab and CHOP, otherwise known as R-CHOP. Now, his risk factors for TLS in this case were the fact that he had widespread disease and marrow involvement. He was a stage 4. He had bulky disease on his chest and PET scan. He had a high LDH level and he also had preexisting renal dysfunction. Therefore, we would have probably classified this patient as having high intermediate risk disease, meaning he's more on the high end of intermediate. The interventions that we did in this patient was to provide adequate hydration, such as giving him 3L/m^2 per day of D5 normal saline, and close monitoring of his electrolytes, BUN, creatinine, uric acid, phosphate and calcium at least every 4 hours, close monitoring of his weight and his urine output, and he, also, because he was in the high intermediate risk range, he was treated prophylactically with rasburicase or the recombinant urate oxidase. He did quite well with this regimen, never developed florid tumor lysis, received his R-CHOP therapy on time and had no evidence of evidence of frank tumor lysis syndrome, despite the fact that he had a number of risky features at his presentation.

Dr. Setty:
If you are just tuning in, you are listening to CME on ReachMD. I'm your host, Dr. Prathima Setty, and I am speaking with Dr. Mitchell Cairo, Chief of Pediatric Hematology, Oncology and Stem Cell Transplantation at Westchester Medical Center. Dr. Cairo, as clinicians, we all benefit from guidelines, so what guidelines or tools are available to help clinicians risk stratify their patients?

Dr. Cairo:
That's a great question, and we tackled this about 10 years ago when Dr. Bishop and I and others convened an International TLS Expert Consensus Panel to develop guidelines and clinical algorithms for patient with risk, and we basically define patients with low risk as having a less than 1% chance for developing TLS, intermediate risk between 1% and 5%, and high risk more or less greater than 5% chance. And in this expert consensus panel, we developed a risk assessment based on the malignant disease type. So the first algorithm, we develop highlighted tumors that are mostly low-risk disease, for the most part solid tumors, with the exception of the solid tumors who are unusually sensitive to chemotherapy; myelomas, most chronic leukemias, with the exception of CLL treated with targeted or biological therapy, which is more of an intermediate risk. The second algorithm was patients really that had acute leukemias divided into acute myeloid leukemia, acute lymphoblastic leukemia and Burkitt leukemia, with risk adjustment based on their white counts and their LDH levels. The third and fourth algorithms were for lymphomas, which were also risk-adaptive for stage and LDH levels, and they were further stratified by age, children versus adults, including stage of disease, bulkiness, as well as LDH levels. The final algorithm we developed adjusts the tumor-based algorithm based on other patient-related factors such as preexisting renal insufficiency. So, therefore, the patients who had pre-existing renal insufficiency were added one extra risk, so if they were originally low-risk, they were upgraded to intermediate risk, and patients who were intermediate risk were upgraded to high-risk. Additionally, patients who also presented with already elevated levels of uric acid, phosphate or potassium also increased their risk status, if they had presentation of these particular abnormalities.

Dr. Setty:
Once clinicians have risk-stratified their patients, what are the recommendations for prophylaxis of TLS?

Dr. Cairo:
So the mainstay of prophylaxis, of course, continues to be hydration, frequent electrolyte monitoring and prophylaxis when appropriate. In general, patients who end up in the algorithm of low-risk disease, meaning very low-risk for developing TLS, may only require adequate hydration, electrolyte monitoring with or without the addition of oral allopurinol for their prophylactic treatment. However, patients with intermediate risk of developing TLS need the previously mentioned monitoring, and then, also, may need to either receive allopurinol without the need of alkalization or they may, as I alluded to in the case earlier, may be benefiting with the administration of rasburicase from prophylaxis. High-risk patients require, as previously mentioned, monitoring and hydration, and these patients absolutely, unless they've had previous allergic reaction or a history of G6PD deficiency, should receive rasburicase at least for one dose and repeated when clinically necessary.

Dr. Setty:
And how do allopurinol and rasburicase work to prevent or treat TLS? How do they differ?

Dr. Cairo:
They actually have different mechanism of action, and whether they actually prevent new uric acid or breakdown uric acid, they have different onsets of action and have different efficacy, drug interactions, and side effects. So, for an example, allopurinol is a competitive binder xanthine oxidase. Xanthine oxidase is required to form uric acid from nucleic acids. If one administers allopurinol, its main effect will be to block the formation of new uric acid. However, the downside is that allopurinol does not reduce the level of preexisting uric acid, and that's, therefore, why we didn't mention it as the treatment. In high-risk cases, it's not a very good option in patients who have

already developed hyperuricemia. Febuxostat is also a new novel xanthine oxidase inhibitor. It could be considered a reasonable choice in patients with renal impairment or have had hypersensitivity to allopurinol. However, on the other hand, rasburicase works completely different. This is a recombinant urate oxidase, it works to convert uric acid to allantoin. Allantoin is very soluble, 10 times more soluble than uric acid is in the urine, and this is the drug we tend to use for in patients who developed hyperuricemia. And in head-to-head trials comparing allopurinol and rasburicase, some of which we did in our group, what you see is a more rapid reduction in uric acid, and an earlier reduction in uric acid, significantly when one administers rasburicase versus allopurinol.

Dr. Setty:
Let's examine another case study in which prevention measures were too late. Dr. Cairo, can you discuss a case from your practice whereby a patient developed clinical TLS?

Dr. Cairo:
Sure, I have many cases of these. I'll just pick out one in particular. This was a 9-year-old male who was diagnosed with stage 4 Group C Burkitt leukemia. He presented with a white count of 35,000 with 30% peripheral blast. He had a presenting LDH of 2500, uric acid level of 18, potassium of 4.9, a phosphate at 9.0, a decreased calcium of 6.8, a BUN of 50, and a creatinine of 2.0. He was treated with standard rituximab plus the French-American- British LMB96 chemotherapy protocol. So this patient presents already with evidence of tumor lysis syndrome. He has evidence of laboratory tumor lysis syndrome, because he has elevated uric acid and phosphate. He also has clinical tumor lysis syndrome, because he already has evidence of acute kidney injury at a grade 2 with his creatinine at 2.0. This patient actually presents with a bona fide oncological emergency. He required an immediate management with hydration, electrolyte monitoring, hyperphosphatemia management with an oral phosphate binder, and because of his severe hyperuricemia, he was managed with recombinant urate oxidase or rasburicase. With this hydration, monitoring, treatment of the potassium and uric acid, the patient did fine. He was able to receive his chemotherapy and his rituximab on time and on schedule, and he's now a long-term, complete response patient who is doing quite well.

Dr. Setty:
What are the recommendations to treat established TLS?

Dr. Cairo:
For most patients, it requires very close monitoring. In many hospitals, that may require an admission to the ICU. In other places, it may be where there's already continuous cardiac monitoring present. As I mentioned, frequent electrolyte, uric acid, calcium phosphate, BUN, creatinine monitoring every 2 to 4 hours, vigorous hydration. As mentioned in the case earlier, patients who present with hyperkalemia and/or hyperphosphatemia should be managed, as I mentioned earlier, and there's a good review on this that we published in the *JCO* in 2008 that gives guidelines on how to treat hyperkalemia and hypophosphatemia. Of course, most patients with TLS will also have hyperuricemia, and unless they've had a past allergy to rasburicase or they have had a history of G6PD deficiency, rasburicase would be the treatment of choice in those patients as well.

Dr. Setty:
Before we wrap up our conversation, can you give us some final clinical pearls?

Dr. Cairo:
The incidence of serious tumor lysis syndrome continues to escalate. The advent of newer agents that result in rapid cell death as we evolve into newer treatment modalities means that we need to be vigilant about risk assessment, monitoring, prophylaxis and treatment of TLS, and, as I said earlier, these many times result in an oncological emergency and decisions, and healthcare providers, and institutions need to be prepared and have algorithms already adapted, and the appropriate drugs and monitoring available to provide top management and treatment when they are faced with patients with high risk or have developed tumor lysis syndrome.

Dr. Setty:
I want to thank our guest, Dr. Cairo, for helping us better understand how to identify patients at risk for developing TLS and the key steps to help us prevent and manage this oncologic emergency. I am your host, Dr. Prathima Setty. Thank you for listening.

Dr. Cairo:
Thank you very much. It's been a pleasure having this discussion with you.

Narrator:
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