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EDUCATIONAL OBJECTIVES

After participating in this activity, clinicians should be better able to

- Explain the pathophysiology of tumor lysis syndrome
- Identify two risk factors for developing tumor lysis syndrome
- Describe the treatment options for preventing as well as treating tumor lysis syndrome

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Managing chemotherapy side effects: Tumor lysis syndrome

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STATEMENT OF NEED/PROGRAM OVERVIEW

Tumor lysis syndrome (TLS) is a potentially serious complication of chemotherapy treatment of some cancers. Nursing assessment and management is essential in the prevention and treatment of TLS. Early diagnosis is critical. TLS is managed through identification of high-risk patients, initiation of preventative therapy, early recognition of metabolic and renal complications, and prompt administration of supportive care. Nurses need to know how to assess a patient's risk of TLS and the treatment goals for successful management.

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Managing chemotherapy side effects: Tumor lysis syndrome

Patients undergoing chemotherapy for hematologic cancers are at risk for this complication. This review can help you learn how to assess their risk.

Risk stratification, prophylaxis, and vigilant monitoring are essential to preventing TLS

KEVIN CURLER, PharmD, MBA, BCPS; LISA A. THOMPSON, PharmD, BCOP

Tumor lysis syndrome (TLS) is a potentially serious complication of treating certain cancers.[1,2] When exposed to chemotherapy, malignant cells die and burst (lyse) releasing the contents of these cells into the bloodstream.[3] Rapid release of these intracellular contents shifts electrolyte concentrations outside of normal physiologic ranges. These alterations in electrolytes can impair organ function and cause temporary or permanent organ damage.

Tumor lysis syndrome is characterized by a combination of hyperuricemia, hyperphosphatemia, hyperkalemia, and hypocalcemia. Complications of TLS can range from mild (nausea and muscle cramps) to serious (cardiac arrhythmia, seizure, and death). Different studies report wide variations in the rates of TLS occurrence. Among the highest was 42%, reported in a study of adults with acute, high-grade non-Hodgkin lymphoma.[4] A study of pediatric patients with non-Hodgkin lymphoma observed

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only a 4.4% total incidence of TLS.[5] Mortality rates due to TLS have been reported as high as 2.5% of patients.[6]

PATHOPHYSIOLOGY

Certain types of malignancies are very sensitive to chemotherapy; when exposed to these cytotoxic agents, tumor cells lyse and release their contents including DNA, proteins, and electrolytes. The DNA released from lysed cells is broken down to uric acid. This breakdown is a multistep process. First, DNAase breaks the DNA down into smaller molecules called *nucleotides*. The purine nucleotides are converted to hypoxanthine. Then, the enzyme xanthine oxidase converts hypoxanthine to xanthine, then to uric acid. Uric acid is not very soluble in the acidic environment of the kidney. If uric acid accumulates, it may form urate crystals in the renal tubules or collecting ducts leading to obstruction. This obstruction can reduce urine output and lead to renal failure.[7] In addition to crystal formation, high levels of uric acid can reduce renal blood flow, increase inflammation, and disrupt the usual regulation of renal function.[7] High urine output helps keep crystals from forming and damaging the kidneys.

One important function of the kidneys is to maintain the balance of potassium, phosphorus, and other electrolytes. Cancer cells release large amounts of potassium and phosphorus when they die. If the kidneys cannot remove these electrolytes fast enough, they can build up to dangerously high levels. Hyperkalemia can lead to cardiac abnormalities, including potentially fatal arrhythmias. When phosphorus is high, it binds to calcium to form crystals. This lowers serum calcium levels, which can lead to confusion, muscle spasms, tetany, or seizures.[1] These calcium phosphate crystals also have the potential to damage the kidney.[8]

DEFINITION OF TUMOR LYSIS SYNDROME

TLS is subdivided into laboratory TLS or clinical TLS. A diagnosis of laboratory TLS is based solely on laboratory findings. The commonly used Cairo-Bishop system defines laboratory TLS as the presence of at least two electrolyte disturbances (**Table 1**). In addition, these abnormalities must occur between 3 days prior to and 7 days after starting chemotherapy.[3]

The Cairo-Bishop system defines clinical TLS as laboratory TLS plus one of the following complications: acute kidney injury (serum creatinine 1.5× upper limit of normal or greater), cardiac arrhythmia, seizure, or sudden death.[3] Approximately 5% to 6% of patients at high risk for TLS will develop acute kidney injury during treatment. Nearly half of those will require hemodialysis.[9] Other possible symptoms of TLS include lethargy, nausea, edema, syncope, fluid overload, and heart failure. While these symptoms do not meet the definition of clinical TLS, they should be monitored and managed according to institutional practice.

TABLE 1. Diagnostic laboratory test values for tumor lysis sydrome[3]

Test	Laboratory value
Calcium	<7.0 mg/dL OR <1.12 mg/dL ionized OR 25% decrease from baseline
Phosphorus	>4.5 mg/dL in adults OR >6.5 mg/dL in children OR 25% increase from baseline
Potassium	>6.0 mmol/L OR 25% increase from baseline
Uric acid	>8.0 mg/dL in adults OR >ULN for children (age dependent) OR 25% increase from baseline

Key: ULN, upper limit of normal.

RISK FACTORS FOR TLS

Tumor lysis syndrome prevention is key to averting organ damage and other complications. The challenge comes with accurately identifying which patients are at highest risk for TLS so appropriate prophylaxis can be prescribed. Researchers and clinicians have worked to develop a standardized method for categorizing a patient's risk of developing TLS. The current evidence suggests that the most important factors are type of cancer, extent of disease, presenting laboratory test values, age, and renal function.[1,2,8]

Different malignancies are associated with different risks of TLS. In general, acute leukemias and lymphomas (particularly Burkitt lymphoma) are associated with the highest risk of TLS.[2,10] Patients with acute leukemia often present with elevated white blood cell count (WBC); these cells are usually very sensitive to chemotherapy. TLS risk is high when a large number of malignant cells are present, and when they rapidly lyse when exposed to chemotherapy.[11] Cases have been reported in which patients with acute leukemia developed TLS even before chemotherapy is started, a condition known as acute spontaneous TLS. Although this condition is very rare, a patient may have laboratory or clinical symptoms of TLS at presentation.

Chronic leukemias, indolent lymphomas, and myeloma are usually associated with lower risk of TLS. Solid tumors pose the lowest risk for TLS. The reason may be that solid tumors are generally less sensitive to chemotherapy, and therefore less likely to lyse, than most hematologic malignancies. Even so, cases of

patients with small cell lung cancer, neuroblastoma, and metastatic breast cancer developing TLS have been reported.[12]

An extensive disease burden has been shown to increase the risk of developing TLS.[10] Extensive disease is often defined as a solid tumor larger than 10 cm, lactate dehydrogenase (LDH) more than two times the upper limit of normal, or leukemia with elevated WBC (more than 50,000 cells/μL for acute myelogenous leukemia [AML], or more than 100,000 cells/μL for acute lymphoblastic leukemia [ALL]). **Table 2** describes the risk stratification for TLS by disease.[8]

Adequate renal function helps maintain electrolytes in their usual physiologic ranges; therefore, patients with poor renal function are at higher risk for developing TLS.[1] Whether patients have impaired renal function prior to beginning cancer treatment or develop kidney injury during treatment, the inability to excrete the contents of lysed cells as quickly as they are released into the bloodstream can lead to TLS.

PROPHYLAXIS AND TREATMENT

An improved understanding of TLS development led to therapies designed to prevent and treat the condition. These treatments focus on maintaining a normal balance of electrolytes in the blood and are designed to maximize kidney function, prevent uric acid formation, and break down existing uric acid.

Hydration Intravenous hydration is the cornerstone of TLS prophylaxis.[13] Increased fluid intake leads to greater urine output, which improves excretion of excess electrolytes. Recommended treatment is to administer 2.5 to 3 L/m^2 of IV fluids every 24 hours to patients at the highest risk of TLS.[1-3] Patients should maintain a urine output of at least 2 mL/kg/hour. Loop diuretics (eg, furosemide [Lasix, generics]) may be considered if hydration alone is not enough to maintain adequate urine output, although this is somewhat controversial and no randomized clinical data support their use.[1,3]

Some cancer centers have given IV fluids containing sodium bicarbonate to increase uric acid solubility and decrease urate crystal formation. This is somewhat controversial, as the resulting increase in urine pH may result in higher serum phosphorus levels and increased formation of calcium phosphate crystals. Clinical evidence either for or against the use of sodium bicarbonate IV fluids is not strong, and phosphorus should be monitored closely in patients receiving sodium bicarbonate IV fluids.[1]

Allopurinol (Lopurin, Zyloprim, generics) Allopurinol inhibits xanthine oxidase, the enzyme responsible for uric acid formation. Xanthine oxidase converts hypoxanthine to uric acid via a two-step process. Allopurinol blocks both steps, decreasing production of new uric acid. It does not, however, break down uric acid that is already formed.

Allopurinol is considered a safe and effective method of minimizing uric acid levels in oncology patients at risk of developing hyperuricemia and TLS. One of the first published reports using allopurinol in patients with leukemia and lymphoma showed a reduction in serum uric acid in 74 of 75 patients. The one patient that did not respond had both renal insufficiency and intestinal obstruction, which may have limited the effectiveness of allopurinol.[14]

The oral form of allopurinol is dosed between 600 to 800 mg/day in two to three divided doses. The maximum dose of the IV formulation is 600 mg/day. Patients should be monitored for potential drug-drug interactions between allopurinol and some chemotherapy drugs.[13] For example, allopurinol inhibits the metabolism of mercaptopurine and azathioprine.[15] Pharmacists should review the patient's chemotherapy and medications to detect these drug-drug interactions.

Rasburicase (Elitek) The human body does not break down uric acid into a more easily excreted compound. Other organisms naturally produce urate oxidase, which breaks uric acid down into allantoin, a compound that is more easily excreted. Recombinant technology has made the manufacture of a therapeutic formulation of urate oxidase (rasburicase) possible. Rasburicase is a potent agent used to

TABLE 2. Risk stratification based on disease

Degree of risk	Disease
High	• ALL with WBC ≥100,000 cells/μL or LDH >2x ULN • AML with WBC ≥50,000 cells/μL • Burkitt lymphoma/leukemia (stage III or IV) • Lymphoblastic lymphoma (stage III or IV) • Any intermediate risk patient with renal involvement or renal insufficiency • Any intermediate risk patient with LTLS
Intermediate	• ALL with WBC <100,000 cells/μL and LDH <2x ULN • AML with WBC 10,000-50,000 cells/μL • Bulky solid tumors • Burkitt lymphoma/leukemia (stage I or II) • Lymphoblastic lymphoma (stage I or II) • NHL with LDH >2× ULN
Low	• AML with WBC ≤10,000 cells/μL • CLL • CML • Hodgkin lymphoma • Indolent NHL • Multiple myeloma • NHL with LDH <2× ULN • Select solid tumors

Key: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CLL, chronic lymphoid leukemia; CML, chronic myeloid leukemia; LDH, lactate dehydrogenase; LTLS, laboratory tumor lysis syndrome; NHL, non-Hodgkin lymphoma; ULN, upper limit of normal; WBC, white blood cell count.

eliminate circulating uric acid. The FDA approved rasburicase for the management of uric acid levels in both adult and pediatric patients at risk of developing TLS.[16]

Rasburicase has been shown to reduce serum uric acid levels faster than allopurinol, and to a higher degree. In a study by Goldman and colleagues, pediatric patients treated with rasburicase had an average uric acid reduction of 86%, versus a 12% reduction for patients treated with allopurinol. A reduction in the uric acid area under the curve (AUC) of 61% was also seen in the rasburicase group. This indicates that the response was sustained over several days.[17]

The labeled dose of rasburicase is 0.2 mg/kg daily for up to 5 days; however, alternate dosing strategies have been studied.[15] The Detroit Medical Center reported administering a single dose of 0.15 mg/kg of rasburicase to patients at high risk of developing TLS.[18] Even 96 hours later, all eight patients had a serum uric acid level below 4 mg/dL. The authors estimate that using a single dose, instead of repeated daily doses, saved their institution more than $100,000 (2003 dollars) on the treatment of those eight patients alone.[18]

Other institutions have used single-dose regimens of rasburicase at lower, fixed (not weight-based) doses. Studies have evaluated one-time doses of 3 to 7.5 mg for adult patients at high risk of developing TLS. These have been shown effective at reducing serum uric acid concentration to safe levels. The responses have also been long-lasting for most patients. Single 3-mg doses of rasburicase have been shown to achieve and maintain normal serum uric acid levels (less than 8 mg/dL) for 48 hours.[19-22] As such, many adult patients are treated with fixed doses of 3 to 6 mg.[13]

A few precautions related to the use of rasburicase should be noted. Because it is a biologic product, patients may develop antibodies against it. These antibodies can trigger an allergic reaction or limit the effectiveness of rasburicase. In addition, rasburicase should not be given to patients with a glucose-6-phosphate dehydrogenase (G6PD) deficiency. G6PD is needed to eliminate the hydrogen peroxide produced when rasburicase converts uric acid to allantoin. Patients with insufficient G6PD are at risk of developing methemoglobinemia and hemolysis. Patients of Asian or African descent are at higher risk for G6PD deficiency. Screening these patients for G6PD is recommended prior to treatment with rasburicase. The biologic has caused fetal damage in animal models, so should only be given to pregnant women if the benefit to the mother outweighs the potential risk to the fetus.[1,2,8]

Rasburicase will continue to break down uric acid in the blood, even after the blood sample is drawn from the patient. Therefore, blood samples drawn from a patient treated with rasburicase should be put on ice immediately and analyzed within 4 hours of collection.[17] Chilling the blood sample reduces the activity of rasburicase. Samples not put on ice will return a falsely low uric acid level.

PROPHYLACTIC RECOMMENDATIONS BY RISK LEVEL

Low risk The initial prophylaxis and monitoring plan depends on the risk of developing TLS. For patients at low risk, adequate hydration to maintain target urine output is usually effective. Allopurinol can be considered for these patients. Monitoring for changes in potassium, phosphorus, uric acid, calcium, and serum creatinine levels should be performed every day, and more frequently if symptomatically indicated.[1,2]

Intermediate risk Patients at intermediate risk for TLS should receive the same aggressive hydration, plus allopurinol. Allopurinol should be started 2 to 3 days prior to chemotherapy, if possible, and continued for 10 to 14 days.[13] Intermediate-risk patients should have their serum calcium, creatinine, phosphorus, potassium, and uric acid levels monitored every 8 to 12 hours initially. Laboratory monitoring can be performed less frequently once the patient has completed 2 days of chemotherapy.[1,2]

High risk Hydration and urine output goals for patients at high risk of developing TLS are the same as for patients at lower risk. Patients at high risk for TLS should receive a single prophylactic dose of rasburicase. The prophylactic dose can be repeated if repeat uric acid levels are elevated. High-risk patients should have their serum calcium, creatinine, phosphorus, potassium, and uric acid levels checked every 4 to 6 hours for the first 2 days of chemotherapy. Laboratory monitoring may be performed less frequently once the patient has completed 2 days of chemotherapy.[1,2]

Some clinicians choose to treat high-risk patients with a *prephase* to lessen the risk of TLS. A prephase can consist of steroid monotherapy or lower doses of the chemotherapy that will be used to treat the cancer. Prephase treatments may last 5 to 7 days.[23,24] The rationale for a prephase is that the lower-intensity treatment will kill cancer cells more slowly than typical chemotherapy regimens, releasing cell contents more slowly with less chance of TLS developing.[1]

Patients who develop laboratory TLS, regardless of their initial risk level, should be treated proactively. Intravenous hydration should be continued at 2.5 to 3 L/m^2/day, if tolerated. Hyperkalemia, hyperphosphatemia, hypocalcemia, and other electrolyte abnormalities should be managed per institutional guidelines. A pharmacist should be consulted to evaluate the patient's medications to determine if any other medications are contributing to the electrolyte disturbances (eg, medications that contain potassium). Patients who develop hyperuricemia, regardless of initial risk stratum, should be treated with

rasburicase at the same dose used for prophylactic dosing. In the event of acute kidney injury, patients may require hemodialysis. TLS can worsen rapidly if left uncorrected, so the threshold for initiating hemodialysis may be lower in patients with TLS than in other patient populations.[1]

CONCLUSION

Tumor lysis syndrome is a serious, potentially fatal complication of cancer treatment. The possible complications of this syndrome can be minimized by proactive risk stratification, prophylactic therapies, and vigilant monitoring. Prevention and treatment of TLS requires frequent assessment of electrolytes and clinical symptoms, as well as administration of fluids and medications. Oncology nurses are vital to the early detection and proper management of TLS. ■

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