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Oncology Emergency series

Recognizing and preventing tumor lysis syndrome

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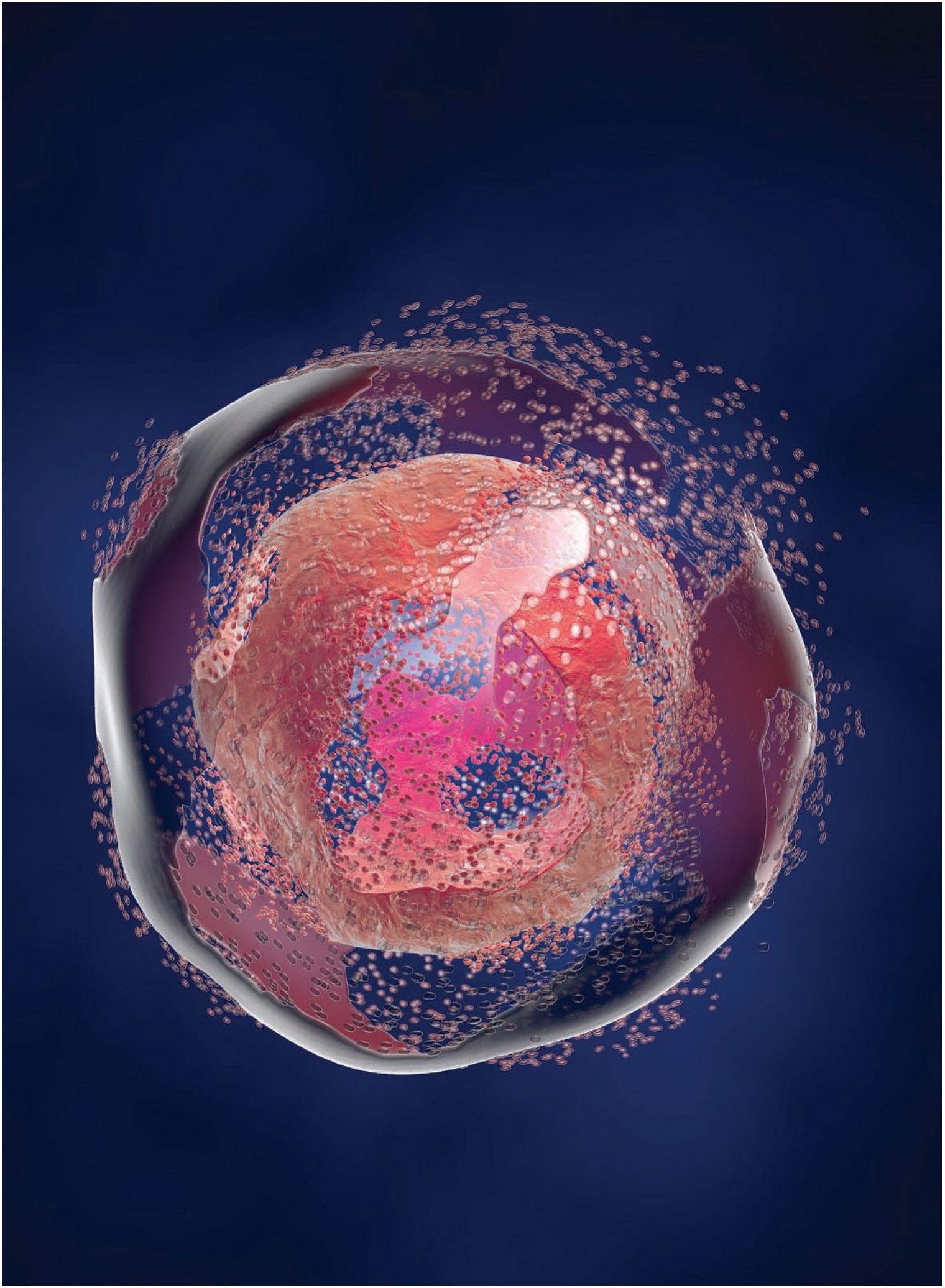
TUMOR LYSIS SYNDROME (TLS) is one of the metabolic oncologic emergencies identified by the Oncology Nursing Society.[1] TLS occurs when a large number of rapidly dividing malignant tumor cells are killed (or lysed), releasing large amounts of their intracellular components, including electrolytes, into the systemic circulation. As a result, TLS can pose potentially life-threatening complications for the patient such as electrolyte imbalances, acute kidney injury (AKI), acid-base imbalances, and possibly death.

After explaining how TLS develops, this article reviews who's at risk, how it's diagnosed, and what steps nurses can take to help prevent this dangerous complication of cancer treatment.

Understanding the pathophysiology

TLS typically develops when a large number of cancer cells are exposed to antineoplastic therapy, which may include chemotherapy, radiation therapy, biotherapy (such as with some monoclonal antibodies), hormonal agents, steroids, or any combination of these.[2] Spontaneous TLS has also been reported when the lab findings described below occur before the patient receives any antineoplastic therapy.[3,4]

TLS is more likely to develop in patients with a high tumor burden (that is, a large tumor with a large number of cancer cells) because the more cancer cells that lyse, the more intracellular components (including potassium, phosphate, and nucleic acids) are released into the bloodstream.[1,2,5-7] This results in complications such as hyperkalemia, hyperphosphatemia, and secondary hypocalcemia; the released nucleic acids are converted to uric acid resulting in hyperuricemia.

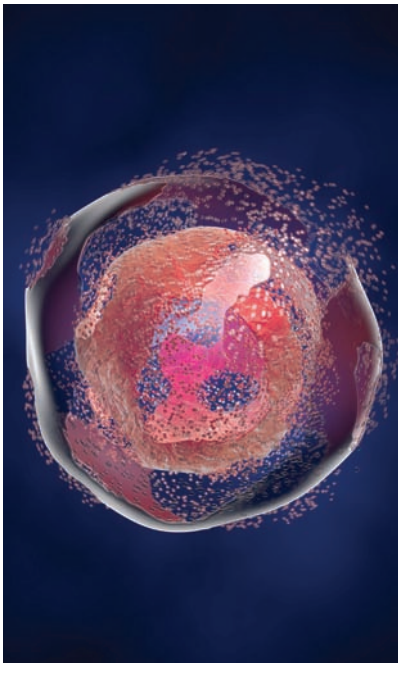


Hyperuricemia and hyperphosphatemia contribute to AKI by promoting formation of uric acid precipitates and calcium phosphate deposits in the renal tubules, renal vasoconstriction, decreased renal blood flow, and inflammation.[3,8]

Who's at risk?

The exact incidence of TLS isn't known; it's unpredictable and disease dependent. In addition, improved TLS prophylaxis has reduced its incidence.[9]

Risk factors associated with TLS can be classified into three categories: patient-related, disease-related, and treatment-related. (See *Risk factors for TLS*.) TLS is most likely to occur in patients who have hematologic malignancies. Burkitt-type non-Hodgkin lymphoma, acute lymphoblastic leukemia, acute lymphoblastic lymphoma, and chronic leukemia are among the malignancies most associated with TLS because they're more likely to have high tumor burden, increased sensitivity to chemotherapy, and rapid cell turnover.[1,5]



TLS is most likely to occur in patients with hematologic malignancies.

Patients at highest risk for TLS have rapidly proliferating malignant tumors that are sensitive to treatment. Elevated serum lactate dehydrogenase (LDH) levels are associated with high tumor volume, a strong predictor of complications associated with therapy.[1] Preexisting renal dysfunction is associated with TLS because lysed tumor cells and their intracellular contents can't be effectively excreted. The patient's health history can also help identify risk factors for TLS. For example, a history of gout with hyperuricemia or a history of renal dysfunction increases the patient's risk of TLS.

Clinical manifestations of TLS

The clinical presentation of TLS is nonspecific and reflects its associated metabolic complications of hyperkalemia, hyperphosphatemia, secondary hypocalcemia, and hyperuricemia. Clinical manifestations include weakness, anorexia, nausea, vomiting, and diarrhea as well as cardiovascular and neuromuscular abnormalities. (See *Signs and symptoms of TLS*.)

Two neurologic signs may be associated with hypocalcemia:

Risk factors for TLS[1,2,5,9,19]

Patient-related factors	Disease-related factors	Treatment-related factors
• dehydration	Large tumor burden or tumor with rapidly dividing cells:	• corticosteroids
• oliguria or anuria	• Burkitt lymphoma	• intrathecal methotrexate
• renal dysfunction	• acute lymphoblastic lymphoma	• tamoxifen
• acidic urine	• acute lymphoblastic leukemia	• rituximab
• leukocytosis	• chronic leukemia	• gemtuzumab
• extensive lymph node involvement	• breast cancer	• alemtuzumab
• hyperkalemia	• T-cell lymphoma	• cladribine
• hyperphosphatemia	• lymphosarcoma	• imatinib mesylate
• large tumor burden	• small cell lung cancer	• cytarabine
• hyperuricemia	• gastric cancer	• etoposide
• increased serum lactate dehydrogenase	• colorectal cancer	• cisplatin
• nephrotoxic agent exposure	• germ cell cancer	• doxorubicin
	• ovarian cancer	• paclitaxel
	• vulvar cancer	• fludarabine
	• thymoma	• mitoxantrone
	• neuroblastoma	• total body irradiation
	• metastatic lymphoma	
	• metastatic medulloblastoma	

Signs and symptoms of TLS[1,19]

Hyperkalemia	Hyperphosphatemia	Hypocalcemia	Hyperuricemia
• diarrhea	• anuria	• muscle twitching	• nausea
• nausea	• oliguria	• carpopedal spasm	• vomiting
• vomiting	• azotemia	• tetany	• diarrhea
• paresis or paralysis	• signs and symptoms of hypocalcemia	• seizures	• peripheral edema
• paresthesias		• laryngospasm	• flank pain
• muscle cramps		• paresthesias	• oliguria
• cardiac conduction defects		• Chvostek sign	• anuria
• cardiac dysrhythmias		• Trousseau sign	• azotemia
• ECG changes*		• confusion	• crystalluria
		• delirium	
		• hypotension	
		• ventricular dysrhythmias	
		• QT interval prolongation	

*The ECG changes of hyperkalemia include tall peaked T waves with a shortened QT interval; progressive lengthening of the PR interval and QRS duration; disappearance of the P wave; and widening of the QRS complex to a sine wave pattern.[20]

Chvostek and Trousseau signs. (See *Two neurologic signs of TLS.*) Chvostek sign isn't a specific sign of hypocalcemia. In fact, about one-third of patients with hypocalcemia don't present with this sign, and about 10% of patients with a Chvostek sign have normal calcium levels.[10]

Key lab findings

The diagnosis of TLS is based on lab data that are consistent with its associated pathophysiologic changes, including hyperkalemia, hyperphosphatemia, secondary hypocalcemia, and hyperuricemia.

Hyperkalemia can develop as soon as 6 hours after the start of antineoplastic therapy.[6] *Hyperphosphatemia* typically develops within 24 to 48 hours after the onset of therapy.[6] *Hypocalcemia* typically occurs 24 to 48 hours after the onset of therapy.[6] *Hyperuricemia* typically develops within 48 to 72 hours after antineoplastic therapy has been started.[1,6,9] (See *Using the Cairo-Bishop definition/classification* for more diagnostic criteria.)

If the patient has a large tumor burden, the serum LDH level will be elevated (as discussed earlier). If the patient has underlying renal dysfunction or develops AKI as a result of TLS, lab findings may include decreased creatinine clearance and estimated glomerular filtration rate (eGFR) and increased blood urea nitrogen and serum creatinine. Arterial blood gases may demonstrate metabolic acidosis. A urinalysis may reveal uric acid crystals.[2]

Treatment strategies

When a patient has been diagnosed with TLS, nursing priorities include assessing and maintaining the patient's airway, breathing, and circulation; monitoring vital signs and cardiac rhythm; assessing for metabolic and electrolyte abnormalities; maintaining optimal fluid status; administering prescribed medications; and providing patient and family education and emotional support. Metabolic and electrolyte abnormalities are managed as follows:

• **Hyperkalemia.** Management of hyperkalemia includes using continuous cardiac monitoring for dysrhythmias, restricting dietary potassium, and administering calcium gluconate or calcium chloride, sodium bicarbonate, regular insulin with glucose, beta-2-adrenergic agonists (such as albuterol), or a combination of these agents. Calcium antagonizes the action of potassium at the cardiac cell membrane. Insulin, sodium bicarbonate, and beta-2-adrenergic agonists drive extracellular potassium into the cells. Glucose is administered with regular insulin to avoid hypoglycemia during insulin administration.

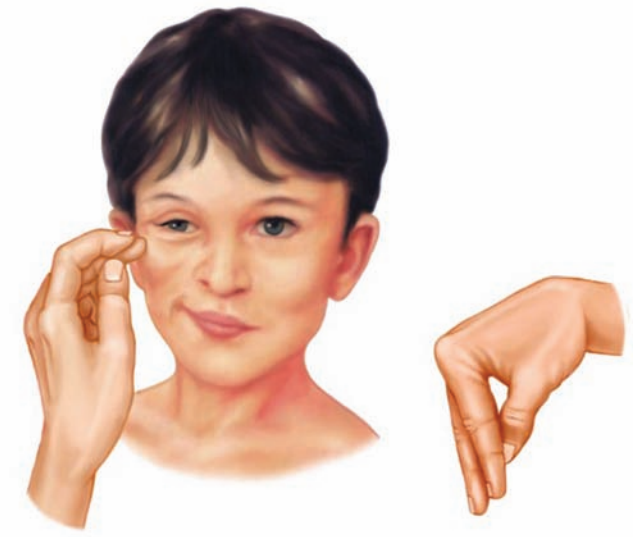
Because the effects of calcium administration and interventions aimed at shifting potassium into the cells are temporary, interventions that remove potassium from the body may also be needed. These include administering a cation exchange resin (sodium polystyrene sulfonate) or a loop or thiazide diuretic, or performing hemodialysis.[11]

Additional interventions include ensuring that the patient doesn't receive I.V. fluids containing potassium or medications containing potassium or contributing to its retention, such as angiotensin-converting enzyme inhibitors.

• **Hyperphosphatemia.** Phosphate binders, such as calcium acetate and aluminum hydroxide, are used to lower serum phosphorus levels by preventing gastrointestinal phosphate absorption. Because of the inverse

Two neurologic signs of TLS

(*Left*) The Chvostek sign: a contraction of the facial muscles elicited in response to a light tap over the facial nerve in front of ear. (*Right*) The Trousseau sign: carpopedal spasm induced by inflating a BP cuff above systolic BP.



relationship between phosphorus and calcium, monitor both serum calcium and phosphorus levels.[3,6,12] Other phosphate binders (such as sevelamer) that don't contain calcium (or aluminum) are also available. As is the case with hyperkalemia, make sure that no medications containing phosphorus are administered. Administering 0.9% sodium chloride solution with a loop diuretic (such as furosemide) may also promote renal excretion of phosphorus.[13]

• **Hypocalcemia**. Nurses should institute seizure precautions for patients with symptomatic hypocalcemia and administer I.V. calcium as prescribed; for those who are asymptomatic, no treatment is generally required.[5]

Measure QT intervals and calculate the QTc at least every shift. Hypocalcemia can cause QT interval prolongation and increased QTc, increasing the risk of ventricular dysrhythmias including torsades de pointes (TdP). TdP is a form of polymorphic ventricular tachycardia that occurs in the setting of QT interval prolongation.[14]

• **Hyperuricemia.** Used in patients at intermediate risk for developing TLS, allopurinol is a xanthine oxidase inhibitor that prevents uric acid buildup by reducing new uric acid production; it doesn't reduce preexisting serum uric acid.[15,16] Allopurinol can interact with several other drugs, including loop and thiazide diuretics. Allopurinol has also been associated with hypersensitivity reactions, including Stevens-Johnson syndrome.[15]

Rasburicase is administered to treat established TLS. Rasburicase is a recombinant urate-oxidase enzyme that converts uric acid to an inactive and soluble uric acid metabolite, reducing plasma levels of uric acid within 4 hours of administration.[13] Rasburicase doesn't prevent uric acid production. The most common adverse reactions to rasburicase when used in patients treated for hematologic or solid tumor malignancy are fever, headache, nausea, vomiting, and hypophosphatemia.[17] Rasburicase is contraindicated in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency because of the risk of severe hemolytic reactions.[17] Screen patients at higher risk for G6PD deficiency (that is, patients of African or Mediterranean ancestry) before starting rasburicase.[3,6,9,12,17] Rasburicase can also cause serious and fatal hypersensitivity reactions including anaphylaxis.[17]

Preventing TLS

Nurses should first identify the patient's risk level for TLS so preventive measures can be instituted 24 to 48 hours before antineoplastic therapy begins.[1] Potentially nephrotoxic medications such as nonsteroidal anti-inflammatory drugs and aminoglycoside antibiotics should be avoided. A diet low in phosphorus and potassium should be instituted.

However, the foundation for preventing TLS is aggressive hydration beginning 24 to 72 hours before antineoplastic treatment is started.[1] The goals of hydration include in-

Using the Cairo-Bishop definition/classification

The Cairo-Bishop definition/classification provides specific lab diagnostic criteria for TLS. Patients must have two or more of the following blood test results:

- potassium greater than or equal to 6 mEq/L (normal, 3.5 to 5.0 mEq/L)
- phosphorus greater than or equal to 4.5 mg/dL (normal, 2.5 to 4.5 mg/dL)
- calcium less than or equal to 7 mg/dL (normal, 8.5 to 10.5 mg/dL)
- uric acid greater than or equal to 8 mg/dL (normal, 2.6 to 8.2 mg/dL).

These lab data must be present within 3 days before or 7 days after beginning antineoplastic therapy.[21] According to The Cairo-Bishop definition/classification, a 25% change from baseline of these lab parameters in the same time frame is acceptable for diagnosing a patient with TLS.[5-7]

Porth CM. *Essentials of Pathophysiology: Concepts of Altered Health States*. Philadelphia, PA: Wolters Kluwer Health/Lippincott Williams and Wilkins; 2007.

creasing urinary output, improving renal perfusion, and helping to prevent calcium phosphate and uric acid precipitates and AKI. The desired urinary output is 2 to 3 L/m^2/day or at least 80 to 100 mL/m^2/hr.[1,5,8]

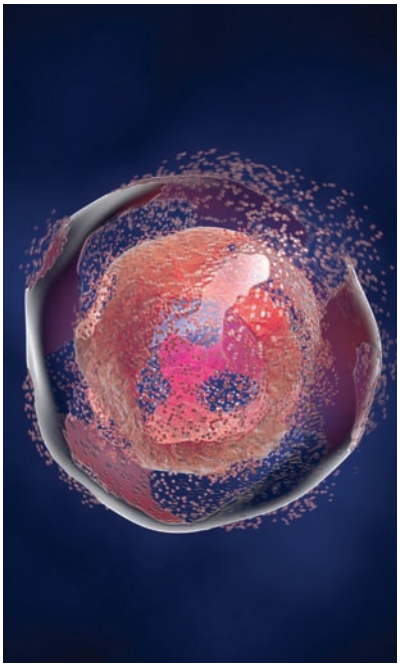
The selection of I.V. fluid depends on the patient's clinical status. For example, for patients with dehydration or hyponatremia, 0.9% sodium chloride solution is generally indicated.[8] The target urine specific gravity is less than 1.010.[18]

Administering allopurinol is another essential element of TLS prevention.[1] Administration of a newer xanthine oxidase inhibitor, febuxostat, may be used in patients with a decreased GFR or in those who have a history of serious reaction or allergy to allopurinol.[7]

Because patients receive up to 3 L/m^2 of fluid in 24 hours for pretreatment hydration, they're at risk for fluid overload. In these cases, administering a diuretic (such as furosemide) may be initiated once fluid resuscitation has been started to help maintain adequate urinary output. Besides increasing urinary output, furosemide helps eliminate potassium, thus decreasing serum potassium levels.[1,13]

Some experts recommend administering a diuretic only in the presence of fluid overload.[7] Using diuretics is contraindicated in hypovolemic patients.[1,8]

In the past, patients also received sodium bicarbonate and/or acetazolamide with their I.V. hydration as urinary alkalinizing agents. The premise of this therapy was to decrease the risk of uric acid crystals forming in the renal tubules. However, more recent data suggest that hydration alone can effectively minimize the risk of uric acid crystallization. Further, alkalinizing the urine increases the risk of hypocalcemia and uric acid nephropathy and formation of calcium phosphate crystals once TLS develops.[7,8] The current recommendation is to administer sodium bicarbonate only in the presence of metabolic acidosis.[5]



The more cancer cells that lyse, the more intracellular components are released into the bloodstream.

Nurses also need to address the psychosocial needs of the patient and family. Patients and families should be taught why the patient is at risk for TLS, including the rationale for each of the preventive measures being implemented. Include the signs and symptoms of TLS and the importance of notifying their healthcare provider immediately if they appear. Developing TLS early in the cancer treatment trajectory can be psychologically stressful for the patient and family, who are already trying to cope with the stress and uncertainty of a cancer diagnosis.

A patient with this oncologic emergency may need to be admitted to the ICU to be monitored for life-threatening dysrhythmias or to treat AKI. If AKI develops, antineoplastic therapy may be temporarily interrupted. Delaying treatment for an aggressive malignant tumor can also be very stressful. Reassure the patient and family that this temporary interruption is essential to decrease the risk of permanent kidney damage.

Collaborating with the hospital's pastoral care service for spiritual and emotional support or the psychiatry department may help facilitate effective coping during this vulnerable period. Some facilities also offer a stress management team experienced in treating the psychological symptoms reported by patients with cancer.

Treating patients with TLS

If prevention strategies aren't completely effective and the patient develops TLS, besides providing emotional support and education to the patient and family, be prepared to institute several nursing interventions. These include collaborating with providers to determine if continuous cardiac monitoring is indicated. If hyperkalemia develops, early recognition and treatment of associated dysrhythmias and other ECG changes are essential.[1,2,5]

Healthcare facilities typically have protocols regarding the frequency for obtaining lab results to detect the presence of TLS. Monitoring of serum electrolytes, uric acid, and renal function studies regularly (often every 4 to 12 hours) is recommended so that trends in the lab data can be identified and patients can be treated earlier.[1,2,5]

I.V. fluid therapy should continue as long as the patient is at risk for the development of TLS. Development of AKI that requires renal replacement therapies is rare. However, if indicated, the patient

may temporarily require renal replacement therapy.[1,2,5]

The big picture

TLS can be a life-threatening complication of malignant tumors with rapidly dividing cells. Meticulous nursing care, including identifying patients at risk, implementing preventive measures, and monitoring the patient's lab results, can help optimize patient outcomes. ■

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