

Tumor Lysis Syndrome

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A 39-year-old man who was recently diagnosed with B-cell acute lymphoblastic leukemia was admitted for induction chemotherapy with a hyper-CVAD regimen (fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone). Three days after the first cycle of chemotherapy, the patient reported worsening fatigue, nausea, and vomiting as well as increased muscle cramps and perioral numbness. His past medical history was significant for hypertension that was well controlled on hydrochlorothiazide. Physical examination revealed stable vital signs and conjunctival pallor, which had been present upon admission. Laboratory studies revealed the following: hemoglobin, 9.2 g/dL; platelets, 73,000 cells/ μ L (92,000 cells/ μ L on admission); white blood cell count, 36×10^9 cells/L; prothrombin time, 10.7 sec; partial thromboplastin time, 35 sec; creatinine, 2.3 mg/dL (0.8 mg/dL on admission); lactate dehydrogenase, 800 mg/dL; potassium, 6.3 mEq/L (4.3 mEq/L baseline); calcium, 6.3 mg/dL (8.7 mg/dL baseline); phosphorus, 7.6 mg/dL (3.3 mg/dL baseline); and uric acid, 15.6 mg/dL (6.3 mg/dL pretreatment level). Urinalysis revealed multiple uric acid crystals. Electrocardiogram revealed a prolonged QT interval, peaked T waves, and normal sinus rhythm. The patient was diagnosed with tumor lysis syndrome based on the laboratory criteria. The patient's fluid infusion was switched from normal saline to sodium bicarbonate 150 mL/hr; he was given 1 g of calcium gluconate and sodium polystyrene sulfonate, 1 ampule of dextrose, and 7 units of insulin intravenously, and he was started on rasburicase. He was also maintained on anti-nauseant medications. Two days after treatment was initiated, the patient's symptoms resolved and his serum creatinine and electrolytes returned to within normal range; however, the uric acid level remained slightly elevated.

Tumor lysis syndrome (TLS) is a collection of metabolic abnormalities that occur as a result of the release of intracellular contents following lysis of malignant cells, typically after initiation of chemotherapy. The features of TLS include hyperphosphatemia, hyperuricemia, hypocalcemia, hyperkalemia, and acute kidney injury. These features are observed when the accumulation of cell degradation byproducts exceeds the clearance ability of the kidneys, resulting in renal damage and further worsening of the aforementioned metabolic disturbances. The incidence of TLS can range from 3% to 22% depending on the patient's risk factors, type of malignancy, and the type of chemotherapeutic agents used.^{1,2} TLS is considered an oncologic emergency given the high incidence of renal failure (25%–38%) and death (5%–14%) associated with its occurrence.^{3–5} This article reviews the diagnosis and treatment of TLS as well as preventive measures that should be taken in at-risk patients undergoing chemotherapy.

RISK FACTORS

Factors associated with the development of TLS include the tumor type and bulk, type of chemotherapy

used in treatment, and preexisting clinical conditions such as kidney disease or dehydration prior to initiation of chemotherapy (Table 1).^{6–8} TLS is commonly seen in tumors with a high mitotic rate and a high response to treatment.^{9–13} It is associated with hematologic and non-hematologic malignancies, although it is most commonly seen with acute leukemias, such as acute lymphoblastic leukemia (ALL), and highly aggressive lymphomas, such as Burkitt's lymphoma (Table 2).^{14–28} TLS is not universal among the hematologic malignancies, as it is not common among patients with follicular lymphoma or chronic lymphoblastic leukemia unless the patient has a high white blood cell count and receives anti-CD20 treatment.²⁹ Patients with large cell lymphoma are at high risk for TLS when presenting with a large tumor bulk or an elevated lactate dehydrogenase level.¹⁸ Risk for developing TLS is highest during the induction of chemotherapy, as the tumor burden is greatest at that time.^{30,31} In theory, any agent with activity against a highly

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TAKE HOME POINTS

- Tumor lysis syndrome (TLS) is an oncologic emergency resulting from the release of intracellular contents of tumor cells, usually after initiation of chemotherapy.
- Patients with hematologic malignancies or bulky solid tumors are at high risk of TLS, especially during induction chemotherapy.
- TLS is diagnosed based on laboratory abnormalities, including acute kidney injury, hyperkalemia, hyperuricemia, hyperphosphatemia, and hypocalcemia.
- Judicious use of intravenous hydration and allopurinol decreases the risk for TLS.
- Rasburicase is used in patients at high risk for TLS or patients who have already developed TLS.
- Serum electrolytes, creatinine, and uric acid should be monitored closely and any abnormalities should be corrected.
- If patients develop TLS with acute kidney injury, dialysis should be considered to prevent further complications.

aggressive tumor can precipitate TLS, although certain agents are more often reported, including cisplatin, cladribine, fludarabine, methotrexate, etoposide, and paclitaxel.⁷ Immune-mediated therapies (eg, interferon alfa-2a/2b and rituximab), corticosteroids, imatinib, tamoxifen, and thalidomide as well as radiation therapy have been reported to precipitate TLS.^{10,32,33}

METABOLIC ABNORMALITIES

Historically, hyperuricemia had been the most common manifestation of TLS, but hyperphosphatemia is now more common due to the increasingly widespread use of allopurinol for prophylaxis against uric acid nephropathy. Hyperphosphatemia causes deposition of calcium phosphate in the renal parenchyma and vessels, and is frequently associated with posttreatment acute kidney injury. Hyperuricemia in TLS occurs due to release of nucleic acid products following lysis of tumor cells, and it remains a common manifestation of the syndrome. Uric acid is more soluble in the urate form when the pH is alkaline due to its pKa value of 5.6.³⁴ High concentrations of uric acid along with the acidic environment of the renal tubules leads to precipitation of uric acid, resulting in obstruction of tubular flow and worsening of renal function.^{18,35}

Table 1. Clinical Features Associated with Tumor Lysis Syndrome

Baseline hyperuricemia
Newly administered chemotherapy
Renal dysfunction
Large tumor burden
Chemosensitivity of the tumor
Volume depletion
Increased baseline lactate dehydrogenase
High tumor cell proliferation rate
High white blood cell count in leukemias

Arrhythmias occur as a result of hyperkalemia in 5% of patients and are the most common cause of death in TLS.¹⁸ Patients can present with the electrocardiographic changes of hyperkalemia, such as peaked T waves, prolonged PR interval, and wide QRS complexes.^{3,18} Hypocalcemia occurs as a result of hyperphosphatemia, which causes deposition of calcium phosphate crystals. Hypocalcemia can lead to tetany, cardiac arrhythmias (enhances cardiac toxicity of hyperkalemia), and muscle cramps.¹ Hypocalcemia with levels less than 6 mg/dL have been observed in patients with TLS secondary to non-Hodgkin's lymphoma.³

DIAGNOSIS

TLS is suspected when a patient with a large tumor burden develops significant uricemia (> 15 mg/dL), hyperphosphatemia (> 8 mg/dL), and acute kidney injury. In contrast to TLS, other forms of acute kidney injury are characterized by a uric acid concentration of less than 12 mg/dL and a phosphate level of less than 6 mg/dL.³⁶ The differential diagnosis of acute kidney injury in similar patients includes urinary tract obstruction by tumors, hypercalcemia of malignancy, prerenal azotemia, renal infiltration by malignant cells, and rarely renal vasoconstriction due to adenosine secretion by malignant cells. The diagnosis of TLS is based on the Cairo-Bishop criteria, which combine laboratory and clinical findings with a grading system to assess the severity of disease (**Table 3**).⁶ The grading system of Cairo-Bishop criteria (0–V) is based on multiple factors, including presence of laboratory TLS criteria, severity of seizures, type of arrhythmias, and the degree of rise of serum creatinine. The severity or the grade does not alter management except by directing attention to any complications (eg, seizure or arrhythmia).

Spontaneous TLS, which occurs prior to treatment with chemotherapy, has been reported in cases of

Table 2. Malignancies Associated with Tumor Lysis Syndrome

Hematologic Malignancies	Solid Tumors
Acute leukemia (most commonly acute lymphoblastic leukemia; 10%) ¹⁷	Breast cancer ²¹
Non-Hodgkin's lymphoma, high grade (6%) ¹⁸	Ovarian cancer ²²
Chronic leukemia ¹⁹	Hepatocellular cancer ²³
Multiple myeloma (2%) ²⁰	Vulvar squamous cell carcinoma ²⁴
	Small cell lung cancer ²⁵
	Medulloblastoma ²⁶
	Sarcomas ²⁶
	Metastatic melanoma ²⁷
	Germ cell tumors ²⁸

leukemia and lymphoma as well as in 1 case of breast cancer.^{37–39} Pretreatment, or spontaneous, TLS is characterized by a lack of hyperphosphatemia, but it otherwise has the same features as posttreatment TLS.³⁸ Highly proliferative tumors release phosphorous and uric acid as a result of rapid nucleoprotein turnover. Utilization of released phosphorous by tumor cells prior to initiation of chemotherapy is believed to be the reason why hyperphosphatemia does not occur in pretreatment TLS.⁴⁰ In posttreatment TLS, rapid cell death secondary to chemotherapy produces increased uric acid and phosphorous levels but the phosphorous is not used for synthesis of new cells.

PREVENTION

The key element in prevention of TLS is to identify patients at risk and implement adequate measures to avoid the precipitation of TLS. The ideal time to implement preventive measures is within 48 hours of treatment with chemotherapy.⁴¹ The first step in prevention of TLS is to minimize the risk factors during the high-risk period, which ranges from 3 days prior to chemotherapy to 7 days postchemotherapy. This includes but is not limited to avoiding medications that will increase the serum levels of potassium, phosphorus, and uric acid (eg, thiazide diuretics and potassium-sparing diuretics). Nephrotoxic agents such as nonsteroidal anti-inflammatory drugs, aminoglycosides, intravenous radiocontrast, and intravenous hydroxyethyl starch should be avoided. In addition, before chemotherapy is initiated, steps should be taken to correct reversible forms of acute kidney injury, such as volume contraction, hypercalcemia, and obstruction.

Prevention of TLS also consists of aggressive intravenous volume repletion (isotonic sodium chloride or sodium bicarbonate) to maintain a urine output of more than 100 mL/hr. Volume repletion typically

Table 3. Cairo-Bishop Criteria for Diagnosis of Tumor Lysis Syndrome (TLS)

Laboratory TLS

2 or more of the following criteria occurring within 3 days before or 7 days after initiation of chemotherapy in a well-hydrated patient who is receiving a hypouricemic agent:

Uric acid ≥ 8 mg/dL (476 $\mu\text{mol/L}$) or 25% increase from baseline

Phosphate ≥ 4.5 mg/dL or 25% increase from baseline

Potassium ≥ 6 mEq/L or 25% increase from baseline

Calcium ≤ 7 mg/dL or 25% decrease from baseline

Clinical TLS

Includes the diagnosis of laboratory TLS plus 1 or more of the following findings:

Increased serum creatinine (1.5 times the upper limit of normal)

Cardiac arrhythmia or sudden death

New-onset seizures

Adapted with permission from Cairo MS, Bishop M. Tumor lysis syndrome: new therapeutic strategies and classification. *Br J Haematol* 2004;127:3–11.

is started within 2 days of starting chemotherapy and is continued for another 2 to 3 days after or until all electrolyte disturbances are corrected.¹⁴ Mannitol and loop diuretics can be used to maintain the target urine output if the patient cannot tolerate high volumes of intravenous fluids due to existing medical problems; however, use of loop diuretics carries the risk of precipitating calcium phosphate and uric acid crystals in the kidney.⁴²

Urinary alkalinization increases the solubility and hence the excretion of uric acid. Alkalinization to maintain the urine pH around 6.5 to 7 can be achieved by using sodium bicarbonate 50 to 150 mEq/L of intravenous fluid or orally.⁴³ However, this intervention has some limitations, including the possibility of fluid overload and the potential of precipitating calcium phosphate crystals in the kidney with coexisting marked hyperphosphatemia. In addition, urinary alkalinization is not necessary when rasburicase is used due to its rapid onset of action. The role of urinary alkalinization is controversial at this time as there is no study to show that alkalinization is superior to volume repletion with isotonic saline alone.⁴⁴

Allopurinol or rasburicase are both approved for the prevention of TLS, with rasburicase reserved for the high-risk population. Allopurinol inhibits xanthine oxidase, thereby preventing the degradation of purines to uric acid and hence hyperuricemia. It is indicated for prophylaxis in patients who are at low risk for TLS. Low-risk patients are defined as those having normal

plasma uric acid, lower tumor burden (lactate dehydrogenase < 2 times normal, white blood cell count < 50×10^9 cells/L), low-intensity therapy, adequate hydration status, and no evidence of kidney infiltration by the tumor.⁶ Allopurinol is approved for intravenous use in patients unable to tolerate oral medications. In the setting of hyperuricemia, allopurinol reaches its peak effect in 5 to 7 days.⁴⁵ Allopurinol is given orally at a dose of 200 to 300 mg/m² daily (maximum dose is 800 mg/day) or intravenously at a dose of 200 to 400 mg/m² daily (maximum dose is 600 mg/day).

Rasburicase is a recombinant urate oxidase enzyme that converts uric acid to allantoin. Allantoin is 5 to 10 times more soluble than uric acid and hence more easily excreted through the kidney. Rasburicase has a much faster action than allopurinol; it can decrease uric acid levels within 4 hours of administration.⁴⁶ Due to the high cost of rasburicase (approximately \$2600 daily), it is used either for prophylaxis of hyperuricemia in patients who are at significant risk for TLS or for the treatment of hyperuricemia in patients with TLS. Candidates for rasburicase have an elevated uric acid level, high tumor burden, hematologic malignancies (ALL, acute myelogenous leukemia, Burkitt's lymphoma), high-intensity therapy, dehydration, and kidney infiltration by the tumor.⁶ Rasburicase has been approved for use in pediatric patients, but its use has been extended to the adult population in daily single or multidose regimens.^{47–49} While the original studies utilized 0.2 mg/kg/day intravenously for 5 to 7 days, recent studies have shown that lower doses (0.05–0.2 mg/kg/day) and shorter treatment duration of 1 to 3 days are as effective as the original regimen and may be more cost-effective.^{50–52} Rasburicase should be avoided in patients with G6PD deficiency due to risk of hemolysis. Rasburicase has also been reported to cause hypersensitivity reactions.⁵³

TREATMENT

The treatment of TLS is directed toward correcting the electrolyte abnormalities of hypocalcemia, hyperphosphatemia, and hyperkalemia. The approach to treatment of acute kidney injury depends upon whether TLS occurs prior to or after initiation of chemotherapy. Urate nephropathy is more likely to occur in the pretreatment period. Acute urate nephropathy, if present prior to initiating therapy, can be treated with rasburicase, intravenous fluids, and possibly a loop diuretic to promote excretion of the uric acid crystals. If hyperuricemia persists and diuresis cannot be maintained, hemodialysis to remove the excess serum uric acid can be considered; the outcome is usually favorable if treatment is initiated early.

In the posttreatment period, hyperphosphatemia is usually the major electrolyte disturbance and precipitant of acute kidney injury. Treatment is directed mainly at lowering phosphorus levels. Hemodialysis achieves rapid correction of hyperphosphatemia. Due to the high burden of phosphorus in these patients, hemodialysis is needed at intervals of 12 to 24 hours. Phosphorus can be cleared at a rate of 9 mg per minute of hemodialysis.⁵⁴ Other methods of dialysis such as continuous venovenous hemodialysis or continuous arteriovenous hemodialysis can be more effective in lowering serum phosphorus levels in such patients.⁵⁵

CONCLUSION

TLS is often seen in high-risk patients after initiation of chemotherapy and is characterized by hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia. Prevention of TLS is important given the potential for poor outcomes once the syndrome develops and involves identifying patients at risk, minimizing precipitating factors, and initiating preventive measures quickly. Aggressive volume repletion (sodium chloride or sodium bicarbonate) with mannitol, if needed, to achieve adequate urine output should be started 2 days prior to chemotherapy. Allopurinol or rasburicase are both approved for the prevention of TLS, with rasburicase reserved for the high-risk population. **HP**

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