A Review of Tumor Lysis Syndrome

ABSTRACT: Tumor lysis syndrome (TLS), an oncologic emergency, results when cancer cells are rapidly lysed after chemotherapy or other treatments. Patients at risk should be rapidly identified and therapeutic measures initiated. Goals are to prevent or treat electrolyte anomalies and to preserve organ function. Effective preventive strategies can minimize TLS and complications even in highest-risk patients.

Tumor lysis syndrome (TLS) is an oncologic emergency frequently encountered in clinical practice. It is characterized by a spectrum of metabolic derangements often including hyperuricemia, hyperphosphatemia with associated hypocalcemia, and hyperkalemia, which occur as a result of rapid cellular lysis of cancer cells. This syndrome is potentially fatal if left untreated; if inappropriately managed, it can impart numerous medical complications and impair organs and systems such as the kidneys, heart, central nervous system, and musculoskeletal system.[1]

The management of patients at risk for TLS begins with identifying those patients most likely to develop the complication. Initiation of preventive strategies to avoid the metabolic abnormalities and acute renal failure associated with TLS is essential for positive patient outcomes. Health care practitioners responsible for the care of cancer patients should have a strong understanding of TLS and how to manage patients throughout the high-risk period. This review will provide an overview of the pathophysiology of TLS, current therapeutic strategies to decrease the likelihood of its development, and some medical interventions aimed at ameliorating complications associated with TLS.

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Epidemiology

TLS was first reported almost 80 years ago, but its incidence remains ill-defined.[1] The most commonly referenced percentages are from Hande and Garrow's 1993 retrospective analysis of 102 adult patients with high-grade non-Hodgkin's lymphoma.[2] Hande and Garrow reported the incidence of TLS—identified through serial measurements of laboratory values—to be 42%, whereas the incidence of clinically significant TLS was only 6% in the same population. A similar occurrence rate has been demonstrated in pediatric patients. Wössman et al reported the incidence of TLS to be 26.4% in children with B-cell acute lymphoblastic leukemia.[3] Reasons for the inability to precisely define TLS incidence include variations in defining the syndrome, variations in anticipating and studying its development in select patient populations, and failure to report all occurrences.[4]

Despite the failure to accurately pinpoint TLS prevalence in cancer patients, recognizing risk factors for its development is vital for managing patients. Predisposing factors can be divided into patient characteristics (TABLE 1), tumor types (TABLE 2), and treatment modalities.[1,4-6] High-risk populations include patients with a high tumor burden and an underlying diagnosis of a highly proliferative tumor, particularly when highly sensitive to definitive treatment consisting of chemotherapy, radiotherapy, hormonal therapy, and/or biological therapy.[4-6] TLS sometimes occurs spontaneously prior to treatment initiation and in patients without recognizable risk factors.[7,8]

Syndrome Summary

***Pathophysiology*[1,4-6,9,10]:** The hallmark pathogenesis of TLS is rapid cell lysis following the administration of cytotoxic therapies. The large amount of intracellular components dumped into the extracellular compartment exceeds the catabolic and excretory capacities of the liver and kidneys. This sharp increase in the concentration of selected cellular components overwhelms the body's normal homeostatic mechanisms, resulting in impaired organ function (such as renal failure) and associated morbidity (such as cardiac dysrhythmias and tetany). The characteristic metabolic anomalies of TLS include hyperuricemia,

Table 1: Risk of TLS Based on Patient Characteristics

- High tumor burden (defined as tumor large in size, LDH >1,500 IU/L, WBC >25,000/mm^3)
- Extensive bone-marrow involvement
- Elevated pretreatment uric-acid levels
- Tumor that is highly sensitive to treatment
- Dehydration
- Decreased urine output
- Acidic urine
- Pre-existing renal dysfunction
- Tumor involvement of the kidney and/or renal vasculature
- Advanced age

TLS: tumor lysis syndrome; LDH: lactic dehydrogenase; WBC: white blood cell.
Source: References 1, 4, 6.

Table 2: Risk of TLS According to Tumor Type

Degree of Risk	Tumor Type
High	Burkitt's lymphoma High-grade non-Hodgkin's lymphoma Lymphoblastic lymphoma T-cell acute leukemia Other acute leukemias
Moderate	Low-grade lymphoma treated with chemotherapy/radiation/corticosteroids Multiple myeloma Breast carcinoma treated with chemotherapy/hormonal therapy Small-cell lung carcinoma Germ-cell tumors (seminoma, ovarian)
Low	Low-grade lymphoma treated with interferon Merkel's cell carcinoma Medulloblastoma Adenocarcinoma of the gastrointestinal tract

TLS: tumor lysis syndrome.
Source: Reference 5.

hyperphosphatemia with associated hypocalcemia, and hyperkalemia.

Definition: Although there is a broad, universally accepted definition of TLS, a uniform, discrete description of this syndrome is lacking. Two schemes to accurately define TLS have been published that characterize TLS according to laboratory features as well as clinical manifestations. The first formal definition was published in 1993 by Hande and Garrow.[2] Although it is the most widely referenced definition of TLS, it has some limitations. First, the definition requires that patients exhibit a 25% change in baseline laboratory values, which does not account for those patients with abnormal values at the time of presentation. Second, changes must occur within 96 hours after the initiation of definitive treatment. Patients who develop TLS prior to treatment or beyond four days of therapy are not covered by this definition.

A modified version of Hande and Garrow's definition was published by Cairo and Bishop in 2004.[4] The goal was to provide clinicians with a clinically relevant definition of TLS that is practical and reproducible, like Hande and Garrow's version. However, Cairo and Bishop broadened the time frame for TLS development (abnormal values and changes could occur from three days before initiating therapy to up to seven days after starting therapy) in an effort to capture more cases; they also stratified patients according to low versus high risk.

Clinical Manifestations and Consequences: Clinical signs and symptoms associated with TLS may include nausea, vomiting, lethargy, edema, congestive heart failure, dysrhythmias, muscle cramps, tetany, paresthesias, back pain, syncope, renal failure, and seizures. Although symptoms may develop upon patient presentation, they are more likely to manifest within 12 to 72 hours after administration of cancer therapy.[1,4,6] Identification of patients experiencing TLS based solely on observation of these signs and symptoms is not advisable since these manifestations may be attributable to the patient's underlying malignancy.

Hyperuricemia, which typically occurs two to three days after initiation of cytotoxic therapy, is a result of the rapid release and catabolism of intracellular nucleic acids.[1,4-6,11] Uric acid is the end product of purine–nucleic-acid catabolism by the enzyme xanthine oxidase. Under normal physiologic conditions, more than 99% of uric acid in the blood is in the soluble ionized form and uric acid is excreted by the kidneys at a rate of 500 mg/day.[4] Secretion of uric acid occurs distal to the renal proximal tubule, as the solubility and excretion of uric acid is favored in alkaline environments. Due to higher-than-normal concentrations of nucleic acids in cancer cells compared with normal cells, the destruction of malignant cells can overwhelm the kidneys' excretory capacity of uric acid. If uric acid remains at high concentrations in acidic conditions, uric-acid crystals may form in the distal tubules and the collecting ducts, resulting in obstructive uropathy and uremia. Conditions that can compound the development of uric-acid crystallization include dehydration, decreased glomerular filtration rate, and acidosis.[1,4,6,9]

Hyperphosphatemia is seen when intracellular phosphorus of malignant cells, which can be as much as four times the concentration in normal cells, is released to the extracellular compartment.[4] Although the kidneys initially respond to the increase in phosphorus concentrations with increased urinary excretion and decreased tubular reabsorption, in time the tubular transport mechanisms become saturated and hyperphosphatemia occurs, usually 24 to 48 hours following initial cellular destruction. The most significant complication resulting from increased concentrations of phosphorus is the formation of calcium phosphate precipitates in the renal tubules, resulting in acute renal failure. Hyperphosphatemia is frequently found in association with hypocalcemia since calcium and phosphorus homeostasis are closely and reciprocally linked.[1,4,9]

The most serious consequence of TLS is hyperkalemia, which usually is seen within six to 72 hours after cytotoxic therapy is initiated. Liberation of intracellular potassium into the extracellular space can quickly overwhelm the kidneys' ability to excrete potassium. High serum concentrations of potassium, which can be exacerbated by renal failure, acidosis, and hypocalcemia, can lead to ventricular arrhythmias and sudden death. Symptomatic patients should be evaluated for dialysis, as this is the most effective method of lowering serum potassium values.[1,4,9]

The development of acute renal failure in the setting of TLS is frequently the result of uric-acid nephropathy and volume depletion. As previously mentioned, patients with TLS can experience precipitation of uric-acid crys-

tals in the kidneys. Volume depletion in the cancer patient is seen frequently and is often multifactorial. Volume depletion can be related to disease or diagnostic evaluation, and reasons for it include vomiting, diarrhea, poor oral intake, insensible losses, and fasting prior to procedures and tests. When a decrease in intravascular volume occurs, the patient may experience a prerenal state, which in turn can lead to increases in tubular uric-acid concentrations.[1,4,9]

Prevention and Treatment

The most effective management strategies target TLS prevention and sequelae associated with TLS. Health care providers must be proactive and a bit overcautious in identifying at-risk patients and initiating protective measures. Attempts to correct metabolic disturbances, especially those that are life-threatening or could prevent initiation of cytotoxic therapy, should be made in a timely fashion.

Aggressive Hydration/Forced Diuresis/Discontinuation of Medications[1,4,9,10]: The first measure undertaken to prevent TLS involves the provision of adequate hydration to 1) increase intravascular volume, thereby decreasing extracellular concentrations of uric acid, potassium, and phosphorus; and 2) enhance renal blood flow to maintain a sufficient glomerular filtration rate and urine output. Ideally, aggressive hydration should be started at least 24 to 48 hours prior to chemotherapy initiation; however, this may not always be feasible, depending on tumor type or the patient's clinical condition. IV hydration should be instituted at a rate to provide patients with 2 to 3 L/m^2/day, which is approximately twice maintenance fluids. The goal of increased hydration, which should continue through the duration of initial cancer therapy, is to maintain urine output at a rate of greater than 100 mL/hour (2-3 mL/kg/hour for pediatric patients) and urine specific gravity of less than 1.010. In patients at high risk for fluid overload (e.g., the elderly, congestive heart failure, renal failure, and so on), fluids should be started, but at a more conservative rate.

If adequate urine output cannot be achieved with IV hydration alone, diuretics may be used to achieve the desired outcome. They also can be used to prevent fluid overload in patients and assist with potassium excretion. Loop diuretics, such as furosemide, are used most commonly to achieve these effects. An alternative diuretic is mannitol (0.5 g/kg/dose IV q 6-8 h).

Another measure that health care providers must institute is the discontinuation of agents that may worsen the patient's condition should he or she experience TLS. Electrolyte supplementation, particularly potassium and phosphorus products, should be discontinued and removed from IV fluids. Medications known to cause electrolyte disturbances—such as angiotensin-converting enzyme inhibitors, which can increase potassium values—should be discontinued and alternative therapeutic recommendations provided to the health care team. Additionally, medications proven to be nephrotoxic (e.g., aminoglycosides, NSAIDs, and the like) should be avoided, if possible, during high-risk periods.

Urinary Alkalinization[1,4,9,10]: Alkalinization of the urine assists in decreasing the incidence of uric-acid nephropathy and subsequent renal failure by reducing uric-acid crystallization. In alkaline environments (pH >7.0), uric acid remains ionized (in the form of urate); thus, it is more water-soluble and more readily excreted by the kidneys. Methods of alkalinizing the urine include the addition of sodium bicarbonate or sodium acetate to IV fluids or the administration of oral acetazolamide (Diamox); both methods require monitoring of patients for signs and symptoms of metabolic alkalosis.

Selection of which method to use to increase urinary pH remains controversial. In general, urinary alkalinization can induce the formation of calcium–phosphate precipitates in the renal microvasculature and tubules. This can cause an obstructive nephropathy that can ultimately increase the chance of acute renal failure by decreasing the glomerular filtration rate. Urinary alkalization can cause a xanthine nephropathy by decreasing the solubility of xanthine, a precursor of uric acid. The use of sodium bicarbonate systemically can lower the amount of circulating calcium by strengthening calcium–phosphate bonding, further exacerbating the hypocalcemia seen in TLS.

Allopurinol[1,4,9,10,11]: A structural analog of hypoxanthine, allopurinol is a competitive inhibitor of xanthine oxidase, an enzyme necessary for purine catabolism. When con-

Table 3: Comparison of Allopurinol and Rasburicase

Comparator	Allopurinol	Rasburicase
Effect on uric acid	Inhibits uric-acid formation	Decreases uric-acid levels
Onset of action	Days	Hours
Relative efficacy	Weak	Strong
Reported drug interactions	Mercaptopurine, azathioprine (among others)	None identified
Dose adjustments	Necessary in the setting of renal dysfunction	None
Black box warnings	None	Anaphylaxis, hemolysis, methemoglobinemia
Contraindications	None	G6PD deficiency
Available formulations	IV and oral (tablets and extemporaneous suspension)	IV
Relative cost	Inexpensive	Expensive

G6PD: glucose-6-phosphate dehydrogenase.
Source: References 1, 4, 6, 9, 10, 12, 17.

verted to its active metabolite, oxypurinol, allopurinol prevents the conversion of hypoxanthine to xanthine and xanthine to uric acid. Although it is effective in preventing the formation of new uric acid and the incidence of uric-acid obstructive uropathy, it has no effect on existing uric-acid levels. Thus, it usually takes at least two to three days from the initiation of allopurinol before a reduction in uric acid is achieved.

Due to its inhibition of xanthine oxidase, allopurinol has some clinical limitations. First, its use may result in a xanthine nephropathy. When the enzyme responsible for the catabolism of xanthine and its precursors is blocked, an increase in the concentration of these compounds is often problematic. Second, allopurinol can interact with medications that rely on xanthine oxidase for their metabolism (e.g., mercaptopurine, azathioprine). Dose reductions of such medications must be made if they are to be used concomitantly with allopurinol.

Urate Oxidase: The enzyme urate oxidase is endogenous to mammals except humans and most primates. Also known as uricase, it is the enzyme responsible for the catabolism of uric acid to allantoin, which is five to 10 times more soluble in urine than uric acid. Uricozyme, a nonrecombinant form of urate oxidase isolated from *Aspergillus flavus*, has been used in Europe since the mid-1970s. Uricozyme has proven efficacy in lowering uric-acid levels more rapidly than in historic controls who had received allopurinol in combination with hyperhydration. However, its use is limited by potential immunogenicity and declining efficacy through production of antiuricase antibodies as well as by serious side effects including allergic reactions, anaphylaxis, and bronchospasm.[4-6, 10,12]

In 2002, the FDA approved a recombinant form of urate oxidase, rasburicase (Elitek), isolated as a cDNA clone from *A flavus* and expressed in *Saccharomyces cerevisiae* to produce large quantities of purified protein.[4-6,12,13] Rasburicase has been proven safe and efficacious in several clinical trials.[14-16] It rapidly lowers uric-acid levels, usually within four hours of administration. Compared with allopurinol, its ability to reduce uric-acid levels is not only faster, but more substantial as well.[15] For a comparison of allopurinol and rasburicase, see **TABLE 3**. Rasburicase is generally well tolerated, the most frequently reported side effects being nausea, vomiting, headache, and fever. It is, however, contraindicated in patients with glucose-6-phosphate dehydrogenase deficiency due to reports of hemolytic anemia and methemoglobinemia in these patients following its use.[4,6,12]

One other disadvantage of rasburicase is its high cost. It is approved for use at a dose of 0.15-0.2 mg/kg IV daily for five days.[12] Some investigators have considered alternative dosing regimens (such as fixed doses of rasburicase or shorter duration of therapy) in an effort to address the high cost of the product.[6,17,18] These dosing schemes are not formally endorsed by the company's product labeling, but they warrant further consideration.

Electrolyte Disturbances: Electrolyte derangements associated with TLS should be addressed in relation to the patient's clinical status and handled on a case-by-case basis. Some electrolyte disturbances may warrant monitoring only, whereas some aberrations may require expeditious interventions to prevent serious morbidity and/or mortality. Each disturbance has its own set of interventions aimed at normalization of serum values and amelioration of clinical sequelae.

Summary

TLS can be fatal if untreated or poorly managed, but clinicians have several effective therapeutic options for managing cancer patients to prevent its occurrence. Patients at greatest risk for TLS should be managed the most aggressively in an effort to achieve positive outcomes. Associated electrolyte disturbances, although not completely preventable, can be lessened if patients are monitored judiciously. If TLS is treated appropriately, the risk of secondary complications, such as renal failure, can be significantly reduced.

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