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Tumor Lysis Syndrome: New Challenges and Recent Advances

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Abstract

Tumor lysis syndrome (TLS) is an oncologic emergency triggered by the rapid release of intracellular material from lysing malignant cells. Most common in rapidly growing hematologic malignancies, TLS has been reported in virtually every cancer type. Central to its pathogenesis is the rapid accumulation of uric acid derived from the breakdown of nucleic acids, which leads to kidney failure by various mechanisms. Kidney failure then limits the clearance of potassium, phosphorus, and uric acid leading to hyperkalemia, hyperphosphatemia, and secondary hypocalcemia, which can be fatal. Prevention of TLS may be more effective than treatment, and identification of at-risk individuals in whom to target preventative efforts remains a key research area. Herein, we discuss the pathophysiology, epidemiology, and treatment of TLS with an emphasis on the kidney manifestations of the disease.

Keywords

Tumor lysis syndrome; Acute kidney injury; Acute kidney failure; Rasburicase; Oncologic emergencies

Introduction

Tumor lysis syndrome (TLS) describes the pathological sequela of the rapid lysis of tumor cells. The shift of potassium, phosphorus, and nucleic acid material into the extracellular space can rapidly overcome existing homeostatic mechanisms, leading to acute kidney failure, arrhythmia, and death. TLS is the most common oncologic emergency, and although commonly seen in the context of initial chemotherapeutic treatment of hematologic malignancies, increasing recognition is being paid to the occurrence of spontaneous TLS and TLS secondary to treatment of bulky solid tumors.^{1,2}

Clinical and Laboratory-Based Definitions of TLS

No uniform definition of TLS has been broadly adopted, but the Cairo-Bishop criteria (Table 1) are commonly used.³ There are several drawbacks to their classification system, especially when TLS is examined through a nephrological perspective. First, this definition

of TLS requires that the patient be initiated on chemotherapy, excluding “spontaneous” TLS from the classification system. Spontaneous TLS has been documented in various malignancies, as detailed below. Second, defining acute kidney injury (AKI) by a creatinine concentration greater than 1.5 times the accepted upper limit for age and sex is not standard and would include many patients with CKD in the absence of AKI. Furthermore, the distinction between “laboratory” and “clinical” TLS is largely academic because most guidelines recommend aggressive treatment of laboratory abnormalities before clinical sequela such as kidney failure develop. The Cairo-Bishop scheme also allows for the grading of TLS severity. The grades of TLS (ranging from 0 to no evidence of TLS, to grade V to death) are assigned based on the severity of clinical complications (eg, nature of arrhythmia, frequency of seizure) experienced. Because treatment guidelines do not vary by grade, these distinctions are perhaps most important epidemiologically.

Epidemiology

The incidence of TLS varies greatly depending on the underlying malignancy. Hematologic malignancies with large, rapidly growing, and chemosensitive cells such as high-grade acute lymphoblastic leukemia (ALL) carry the greatest risk. More than 1 in 4 children with that malignancy will develop TLS after treatment.⁴ Among adults, TLS is commonly seen after treatment for ALL, acute myeloid leukemia, and Burkitt’s lymphoma.^{5–7} Although TLS is often associated with cytotoxic chemotherapy, reports exist of TLS occurring after treatment with radiation therapy,^{8,9} dexamethasone treatment,¹⁰ thalidomide therapy,^{11,12} and with newer chemotherapeutic agents including bortezomib and rituximab.^{13–15}

Table 2 describes relative risk of TLS in various hematologic and nonhematologic malignancies. The highest risk of TLS is seen in large-volume, highly metabolic malignancies such as B-cell ALL and Burkitt’s lymphoma, whereas solid tumors and slow-growing hematologic malignancies (such as multiple myeloma) carry lower risks. Most, although not all, cases of TLS with multiple myeloma have followed treatment with bortezomib.¹⁶

Spontaneous TLS

Increasingly documented in high-grade hematologic malignancies, particularly Burkitt’s lymphoma, the triggers for spontaneous TLS have not been well described.^{1,17,18} No prospective studies monitoring for the spontaneous development of TLS exist, limiting our ability to identify risk factors. Some have suggested that uric acid nephropathy is a neglected cause of kidney failure among cancer patients.¹⁹ Although we do not routinely screen cancer patients for the presence of TLS, we do recommend considering TLS in the workup of patients with malignancy and acute kidney failure of undetermined etiology, regardless of their prior treatment status.

TLS in Solid Tumors

Although quite rare, increasing numbers of case reports documenting TLS in solid malignancies have been published over the last decade. This may be due to increased

efficacy of treatment or increased surveillance, but it is clear that the risk of TLS is not limited to individuals with hematologic malignancies.

Phosphate, potassium, and nucleic acid content differ by malignant cell type, but rapid lysis of any cell will lead to a significant shift of these substances to the extracellular space. Recent case reports have documented TLS in patients with hepatocellular carcinoma²⁰ and metastatic prostate cancer,²¹ and earlier studies have reported TLS in various solid tumors.²² Highlighting the fact that any rapidly lysing cell can give rise to this pathologic syndrome, a recent case series has documented a TLS-like hyperuricemic state after antibiotic initiation for visceral leishmaniasis.²³

Although medical prophylaxis of TLS is not the standard of care for patients undergoing treatment of solid tumors, TLS should be considered in the differential diagnosis of any patient with AKI and a significant burden of malignant disease, particularly in the setting of hyperuricemia, hyperkalemia, and hyperphosphatemia.

Predicting TLS

Identifying individuals at risk of TLS would allow for more appropriate prophylaxis. Risk stratification currently centers around the underlying malignancy, but other patient factors clearly increase the likelihood of TLS. Of interest to the nephrologist, TLS is much more common among patients with preexisting kidney disease. A study of nearly 1200 pediatric patients with non-Hodgkin's lymphoma revealed that, of the 63 who developed TLS, 43 had evidence of kidney dysfunction on admission, although the etiology of kidney dysfunction was unclear.²⁴ Among a group of 772 adult patients with a new diagnosis of acute myeloid leukemia, of who 130 developed TLS, pretreatment creatinine concentration greater than 1.4 mg/dL was strongly predictive of the development of TLS in unadjusted and adjusted models, with an odds ratio of 10.7 (4.5–25.1).²⁵ Pathophysiologically, preexisting kidney dysfunction would lead to decreased excretion of uric acid, greater serum uric acid levels, and subsequent kidney injury via mechanisms described below.

Other factors predictive of the development of TLS include pretreatment elevations in uric acid level, lactate dehydrogenase, male gender, and (in hematologic malignancies) splenomegaly.^{4,25–28}

Mortality

In general, TLS is more common among patients with more severe underlying disease, but it is also a marker of therapeutic efficacy. No randomized trials of TLS therapy examine mortality as a primary outcome, but the development of AKI associated with TLS is clearly a strong predictor of death. Among 63 patients with hematologic malignancies and TLS, 6-month mortality was 21% among those without AKI and 66% among those with AKI.²⁹ This relationship persisted after multivariable adjustment ($P = .0006$). Prevention of AKI may be possible with prompt recognition of TLS and appropriate therapy as discussed below. Given the association between AKI and mortality in this condition, prevention of AKI may be the single best target for therapy.

Pathophysiology

Although the rapid release of electrolytes from intracellular stores to the extracellular space can have fatal consequences, usual homeostatic mechanisms can often compensate for these shifts provided that kidney function remains robust. Thus, AKI is central to the development of TLS. This injury is often caused by acute uric acid nephropathy (due to the metabolism of liberated nucleic acids), but it may also be mediated by uric acid-independent mechanisms, including the parenchymal and tubular deposition of calcium-phosphate salts.³⁰

Acute Uric Acid Nephropathy

The purines adenine and guanine are metabolized via a series of steps to the purine base xanthine.³¹ Xanthine is further metabolized by xanthine oxidase to uric acid. Humans, unlike most mammals, lack urate oxidase, an enzyme that metabolizes uric acid to allantoin, a much more soluble substance. The purine metabolic pathway is illustrated in Figure 1.

Urate nephropathy was classically thought to be driven by the precipitation of uric acid crystals in the renal tubules, leading to micro-obstruction and decreased glomerular filtration rate (GFR). Although this may be the primary driver of kidney dysfunction in hyperuricemic states, crystal-independent mechanisms may also exist.³² A seminal work by Conger and colleagues suggested that, in addition to micro-obstruction, hyperuricemia also has marked kidney hemodynamic effects. In a rat model, Conger and colleagues demonstrated marked increases in proximal and distal tubular pressures in rats given exogenous uric acid loads along with a uricase inhibitor-confirming micro-obstruction. In addition, hydrostatic pressures in the peritubular capillaries were increased 2-fold, and vascular resistance distal to the peritubular capillaries was increased by more than 3-fold.³³

Uric acid may also be directly nephrotoxic through various mechanisms. Uric acid scavenges nitric oxide, which can lead to vasoconstriction and kidney ischemia.³⁴ It is also proinflammatory in that vascular smooth muscle cells exposed to uric acid upregulate production of various cytokines, including monocyte chemoattractant protein-1 and tumor necrosis factor- α , which lead to white cell chemotaxis and tissue injury.³⁵ Finally, uric acid inhibits proximal tubular cell proliferation, potentially prolonging kidney injury once it occurs.³⁶

Hyperkalemia

Intracellular potassium concentration can be as high as 120 meq/L.^{37,38} The liberation of potassium from lysing tumor cells can amount to a supraphysiologic potassium load, particularly in the case of hematologic malignancies with a large burden of disease. Under usual conditions, acute potassium loads are taken up into liver and muscle cells, and excess potassium is gradually excreted via kidney and gastrointestinal mechanisms. Among patients with CKD or AKI, potassium clearance is limited and the risk of clinically significant hyperkalemia is greatly increased.³⁹ Hyperkalemia may present as muscle weakness and, if left untreated, it can lead to cardiac arrhythmia and death.

Hyperphosphatemia and Hypocalcemia

Because of the relatively high intracellular phosphate concentration, TLS can induce a large phosphate load to the extracellular space. Similar to potassium, kidney elimination of phosphate may be limited by AKI or preexisting CKD. Hyperphosphatemia may be less common in spontaneous TLS than in that induced by cytotoxic therapies.^{17,19,40,41} This may be because actively growing tumor cells rapidly take up extracellular phosphate liberated from dying tumor cells, causing the net phosphate flux to be neutral.

Hyperphosphatemia leads to morbidity and mortality primarily through chelation with calcium, leading to hypocalcemia and the potential for calcium-phosphate salt deposition in soft tissues (including the kidney). In fact, TLS has been documented in animals that express urate oxidase, presumably due to nephrocalcinosis.^{42–44} It is worth noting that, despite the current availability of recombinant urate oxidase (discussed below), TLS may still lead to AKI due to non-uric-acid-mediated processes.

The secondary hypocalcemia of TLS is the more immediately threatening of the 2 electrolyte disorders, leading (in severe cases) to arrhythmia, seizures, tetany, and death. The hypocalcemia of TLS may persist even after phosphate levels normalize, presumably because of acute deficiencies of 1,25-vitamin D.⁴⁵ Whether this effect is mediated by acute upregulation of fibroblast-growth factor 23 during the hyperphosphatemic period has not been evaluated.⁴⁶

Prevention

Accurate risk assessment is vital to the successful application of prophylactic measures among patients thought to be at risk of TLS. Current guidelines classify risk on the basis of the underlying malignancy, but clinical trials have not been performed to demonstrate superiority of any specific prophylactic regimen on the basis of any other patient characteristic. Therefore, individualization of prophylaxis is appropriate. Given that rapid clearance of liberated intracellular solutes is the key to prevention of AKI (and further decrease in solute excretion), methods to increase GFR and urine output are appropriate regardless of risk category. We recommend patients receive at least 3 L of oral or intravenous fluid daily before initiation of chemotherapy, provided they have no contraindications to volume expansion.^{47,48} In addition, avoidance of kidney vasoconstrictive substances such as nonsteroidal or anti-inflammatory drugs and iodinated contrast is a reasonable, although not evidence-based, consideration.

Among patients at medium or high risk of development of TLS, a prophylactic xanthine oxidase inhibitor should be provided. Even among patients with low-risk tumor types, xanthine oxidase inhibition should be considered if other risk factors (elevation of baseline uric acid or lactate dehydrogenase, or underlying kidney disease) are present.

In patients with high-risk tumor types, consensus guidelines suggest the prophylactic use of recombinant urate oxidase before chemotherapy. Although this treatment clearly lowers the serum uric acid, it has not been definitively shown to improve more relevant clinical

outcomes. Nevertheless, we do recommend prophylactic use of rasburicase in patients in whom a delay of chemotherapy (due to hyperuricemia) might compromise care.²⁸

Management

Volume Expansion

Once TLS has developed, efforts should be made to reestablish normal concentrations of extracellular solutes. Provided that there has not been a complete loss of kidney function, volume expansion, with a goal of increasing kidney excretion of these solutes, is the bedrock of TLS therapy.^{49,50}

In addition to augmenting potassium, phosphate, and uric acid excretion, a robust urine flow rate will decrease the calcium-phosphate product in the renal tubules, decreasing the risk of crystal formation and micro-obstruction. As we discuss above, we agree with current consensus statements suggesting a target fluid intake of 3 L per day, barring contraindications.

Diuretics

Although the use of diuretics to enhance urinary flow rate may be expected to decrease the risk of tubular calcium-phosphate precipitation, this practice has not been studied. Furthermore, the hemodynamic changes associated with diuretic use may further compromise kidney function in this population.⁵¹ Barring clinically important volume overload, we do not routinely use diuretics in the care of patients with TLS.

Allopurinol

Allopurinol is a structural isomer of hypoxanthine. It is metabolized by xanthine oxidase to oxypurinol, the active form of the drug. Oxypurinol is excreted by the kidneys, leading to concerns about dosing in patients with CKD and AKI. Because oxypurinol inhibits the conversion of xanthine to uric acid, allopurinol treatment can elevate serum and urine xanthine levels.⁵² Xanthine is poorly soluble and may lead to crystal formation in the renal tubules, worsening GFR.^{53,54} Although allopurinol decreases the generation of uric acid, it may not improve existing hyperuricemia. As such, it is a reasonable choice for prophylaxis of patients at risk of TLS, although it may be less effective in TLS treatment.⁵⁵

Allopurinol and oxypurinol have been associated with several hypersensitivity syndromes, which has limited enthusiasm for their use, particularly in patients with reduced kidney function. These syndromes range from a relatively benign rash to the life-threatening “allopurinol hypersensitivity syndrome”—a constellation of rash, acute hepatitis, and eosinophilia.⁵⁶ A concern for the development of hypersensitivity has led to the practice of reducing the dose of allopurinol in patients with kidney dysfunction, although it has not been demonstrated that this reduces the risk or severity of allopurinol hypersensitivity reactions. A small cohort study of 120 patients with gout examined those who received “renally dosed” allopurinol vs those who received a standard dose and found no increased rate of hypersensitivity reaction in the standard dosing group.⁵⁷ A case-control study aimed at determining risk factors for allopurinol hypersensitivity syndrome determined that the

presence of CKD was a significant risk factor, but the dose of allopurinol was not.⁵⁸ These findings are difficult to reconcile because higher dose and worse kidney function would be expected to increase serum concentrations of allopurinol, and larger studies are likely needed to determine appropriate dosing of this agent. Early studies of skin testing and lymphocyte hypersensitivity assays failed to identify patients at risk of allopurinol hypersensitivity syndrome.^{59,60} Although care should be taken when initiating this drug in patients with CKD, dose reduction may not be necessary.

It should be noted that an interaction between allopurinol and azathioprine (often used for immunosuppression in patients with transplants or autoimmune conditions) can lead to severe and life-threatening bone marrow suppression.⁶¹ The combination of these agents should be avoided.

Febuxostat

Febuxostat is a novel xanthine oxidase inhibitor that does not appear to have the hypersensitivity profile of allopurinol. In addition, it is metabolized to inactive metabolites in the liver, obviating the need for specific kidney dosing.⁶² Although no clinical trials examining febuxostat in the prevention of TLS have completed, 1 trial is actively recruiting (clinicaltrials.gov NCT01724528) and encouragingly uses kidney function as a primary endpoint.

Febuxostat is efficacious in terms of reducing gout flares and maintaining normal serum uric acid levels.^{63,64} As a xanthine oxidase inhibitor, the risk of xanthine stone formation is likely to be similar to that of allopurinol. Febuxostat is much more costly than the generically available allopurinol, limiting its use. However, in patients with impairments of kidney function or hypersensitivity to allopurinol, febuxostat may be a reasonable choice for TLS prophylaxis until clinical trial results are available.

Urinary Alkalinization

The solubility of uric acid is highly pH dependent. At a typical acidic urine pH of 5.0, the solubility of uric acid is 15 mg/dL vs 200 mg/dL at a pH of 7.0. A neutral urine pH may be achievable via the administration of bicarbonate with or without a carbonic anhydrase inhibitor, but this strategy has not proven efficacious in animal models of TLS.³³ Furthermore, alkalinization of the urine (or serum) can favor the precipitation of calcium-phosphate salts in soft tissues and renal tubules, potentially worsening kidney failure. Beyond that, a more alkaline serum pH decreases ionized calcium levels via increased albumin-calcium avidity, potentially worsening existing hypocalcemia and precipitating tetany. Finally, in the era of recombinant urate oxidase (see below), augmenting urinary clearance of uric acid does not hold the same primacy in TLS treatment. Urinary alkalinization should only be considered in cases of severe hyperuricemia in which recombinant urate oxidase is unavailable. Even in that situation, careful and frequent attention to ionized calcium levels is warranted. In most cases, we do not recommend attempting to alkalinize urine in patients with TLS.

Recombinant Urate Oxidase

Rasburicase (Elitek, Sanofi-Aventis) was approved by the U.S. Food and Drug Administration in October of 2009 for the initial management of plasma uric acid levels in adult patients with leukemia, lymphoma, and solid tumor malignancies who are receiving anticancer therapy expected to result in tumor lysis and subsequent elevation in uric acid.^{55,65} Rasburicase is an *Aspergillus*-derived recombinant urate oxidase and catalyzes the conversion of uric acid to allantoin, carbon dioxide, and hydrogen peroxide. The latter can lead to devastating methemoglobinemia and hemolytic anemia in individuals with glucose-6-phosphate dehydrogenase deficiency.⁶⁶ Rasburicase is active *ex vivo*; blood samples for uric acid should be kept on ice until processed to avoid erroneous measurements.

To date, there have been 6 rasburicase trials, of which 3 were rasburicase vs rasburicase studies examining differences in dosing.^{65,67–71} In all of these studies, the primary outcome was the reduction in serum uric acid concentration, and rasburicase is clearly highly efficacious by this metric. A recent meta-analysis of the use of rasburicase in adults confirmed this efficacy, but it noted a lack of clinical outcome data to support the routine use of the drug.⁷² However, the trials were largely underpowered to detect meaningful differences in clinical endpoints. In the study by Cortes and colleagues, rasburicase was superior to allopurinol in terms of achieving a uric acid level less than 7.5 mg/dL at day 3 to 7. However, rates of kidney failure did not differ between the study arms.⁶⁵ In a pediatric study by Goldman and colleagues again comparing rasburicase to allopurinol, there was a suggestion of improved serum creatinine concentration in the rasburicase group, but the authors did not perform formal statistical tests on this finding.⁷⁰ Despite a lack of data regarding hard endpoints, rasburicase is recommended for treatment of hyperuricemia associated with TLS and for prophylaxis of TLS when chemotherapy is initiated in patients with high-risk malignancies.

Although rasburicase is well tolerated (adverse events occurred in <5% of patients in the largest adult trial),⁶⁵ it is very expensive (up to \$3600 per 7.5-mg vial). The manufacturer-recommended dose is 0.15 to 0.20 mg/kg per day for a total of 5 days during the initiation of chemotherapy. Given the cost associated with such a dosing schedule, there is great interest in alternative dosing strategies. There have been multiple cohort studies that suggest that 1-time dosing (generally at 0.15 mg/kg) will consistently suppress uric acid levels in patients at risk of or who develop TLS.^{68,73–84} A recent randomized trial demonstrated that a single dose of 0.15 mg/kg before the onset of chemotherapy with a rescue dose as needed was as effective as 5-day dosing in normalizing serum uric acid levels.⁷¹ If a 1-time dosing strategy is pursued, uric acid levels should be followed closely (and measured on ice) with repeat dosing initiated if levels rise above 8.0 mg/dL.⁸⁵ Future studies will be needed to evaluate the cost-effectiveness of rasburicase vs more traditional TLS therapy (such as allopurinol). A Cochrane review in 2010 examined the evidence for the use of rasburicase in randomized trials. The review concluded that, although efficacious in terms of reduction in uric acid, no trial has demonstrated improvement in terms of prevention of AKI or mortality. The Cochrane consensus recommendation was that clinicians should weigh the benefits and risks of urate oxidase treatment in patients with hematologic malignancies.⁸⁶ As noted above,

given that adverse reactions are rare, the primary risk with rasburicase treatment seems to be the cost and subsequent strain on the health-care system. Given that clinicians are traditionally cost-agnostic when providing therapy, the need for randomized trials of rasburicase therapy targeting clinical endpoints is greater than ever.

Parenteral/Enteral Calcium

Treatment of TLS-associated hypocalcemia is generally contraindicated in the absence of clinical manifestations of hypocalcemia (tetany, electrocardiogram changes, seizure). Because the hypocalcemia is secondary to hyperphosphatemia, administration of calcium is thought to increase the calcium-phosphate product and thus the rate of calcium-phosphate deposition in tissues, which may potentially worsen AKI. Therefore, efforts to augment clearance of phosphate (which often takes the form of dialytic modalities) should be considered before calcium administration unless the clinical situation is dire.

Dialytic Modalities

In the setting of severe AKI, kidney clearance of potassium, uric acid, and phosphorus is markedly reduced, often resulting in a need for extracorporeal clearance. Given the fact that there is ongoing liberation of these substances from lysing tumor cells, continuous modalities are often preferred to intermittent hemodialysis to reduce the risk of “rebound” hyperkalemia or hyperphosphatemia. That said, the minute-for-minute clearance of potassium is superior with conventional hemodialysis. Therefore, we recommend early hemodialysis for the treatment of life-threatening hyperkalemia, immediately followed by a continuous renal replacement therapy (CRRT) to prevent rebound of hyperkalemia. In the face of robust potassium liberation, prolonged hemodialysis sessions or CRRT at a high dialysate or replacement fluid flow rate (>3–4 L/hr) may be necessary to maintain effective control of serum potassium concentrations.^{87,88}

Because phosphate clearance with dialytic therapy is time dependent, CRRT may be the preferred modality for patients with severe hyperphosphatemia.^{87,89,90} The role of prophylactic CRRT in children and adults at high risk of TLS was examined in 2 small proof-of-concept studies.^{91,92} Although the results were encouraging, larger randomized studies will be needed to assess the benefit of this strategy.

Conclusion

TLS is a potentially devastating consequence of the successful treatment of various malignancies. Although once thought to occur only in particular hematologic cancers, it is clear that (particularly as chemotherapeutics for solid tumors improve) the condition arises in various patients. Kidney disease may be a major risk factor for the condition; thus, the efforts of nephrologists before and after the initiation of cancer therapy may dramatically alter the clinical course. Novel recombinant urate oxidases have changed the landscape of therapy for TLS, but dialytic modalities have their place in the treatment of electrolyte and other disturbances that may arise in the clinical course. The appropriate application of these therapies is likely to reduce the morbidity and mortality associated with this most common of oncologic emergencies.

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CLINICAL SUMMARY

- TLS is common in certain hematologic malignancies, but it may occur even in solid tumors.
- Patients with underlying kidney disease appear to be at increased risk.
- Prevention depends on accurate assessment of risk factors, which may extend beyond the type of malignancy.
- The use of rasburicase, a recombinant urate oxidase inhibitor, is common but has not been robustly studied.

Figure 1.
Purine metabolism. Uric acid is the endproduct in humans.

Table 1**Cairo-Bishop Definitions of Laboratory and Clinical Tumor Lysis Syndrome³**

Laboratory tumor lysis syndrome

Requires 2 of the following criteria achieved in the same 24-h period from 3 days before to 7 days after chemotherapy initiation:

- Uric acid 25% increase from baseline or 8.0 mg/dL
- Potassium 25% increase from baseline or 6.0 meq/L
- Phosphorus 25% increase from baseline or 0.5 mg/dL (6.5 mg/dL in children)
- Calcium 25% decrease from baseline or 7.0 mg/dL

Clinical tumor lysis syndrome

Laboratory tumor lysis syndrome + 1 of the following:

- Creatinine >1.5 times the upper limit of normal of an age-adjusted reference range
 - Seizure
 - Cardiac arrhythmia or sudden death
-

Other causes of AKI should be excluded.

Table 2

Reported Incidences of Tumor Lysis Syndrome Stratified by Risk Category

Malignancy	Reported Incidence (%)
High risk	
Acute lymphocytic leukemia ^{27,28}	5.2–23
Acute myeloid leukemia with white blood cell count >75,000 ²⁵	18
B-cell acute lymphoblastic leukemia ⁴	26.4
Burkitt's lymphoma ⁴	14.9
Intermediate risk	
Acute myeloid leukemia with white blood cell count 25,000–50,000 ²⁵	6
Diffuse large B-cell lymphoma ⁹³	6
Low risk	
Acute myeloid leukemia with white blood cell count <25,000 ²⁵	1
Chronic lymphocytic leukemia ⁹⁴	0.33
Chronic myelogenous leukemia ⁹⁵	Case reports
Solid tumors ²²	Case reports

Risk category as per Cairo and colleagues.⁵⁵