

## Onco-Nephrology: Tumor Lysis Syndrome

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### Summary

**Tumor lysis syndrome (TLS) describes the clinical and laboratory sequelae that result from the rapid release of intracellular contents of dying cancer cells. It is characterized by the release of potassium, phosphorous, and nucleic acids from cancer cells into the blood stream, with the potential to cause hyperkalemia; hyperphosphatemia and secondary hypocalcemia; hyperuricemia; AKI; and, should usual homeostatic mechanisms fail, death. TLS most commonly follows treatment of hematologic malignancies, such as acute lymphocytic or lymphoblastic leukemia, acute myeloid leukemia, and Burkitt lymphoma, but also occurs after treatment of other bulky or rapidly growing tumors, particularly if the patient is highly sensitive to the effects of cytotoxic chemotherapy. Prevention and treatment depend on prompt recognition of patients at risk, volume repletion, allopurinol, rasburicase (a novel recombinant urate oxidase), and, when indicated, dialysis.**

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### Introduction

Tumor lysis syndrome (TLS) describes the clinical and laboratory sequelae that result from the rapid release of intracellular contents of dying cancer cells. It is the single most common oncologic emergency and a frequent source of inpatient consultation for nephrologists (1). TLS is characterized by the release of potassium, phosphorous, and nucleic acids from cancer cells into the blood stream, with the potential to cause hyperkalemia; hyperphosphatemia and secondary hypocalcemia; hyperuricemia; AKI; and, should usual homeostatic mechanisms fail, death. TLS most commonly follows treatment of hematologic malignancies, such as acute lymphocytic or lymphoblastic leukemia, acute myeloid leukemia, and Burkitt lymphoma, but also occurs after treatment of other bulky or rapidly growing tumors, particularly if highly sensitive to the effects of cytotoxic chemotherapy (2–4). TLS has been reported after treatment with conventional chemotherapy, dexamethasone (5), and newer agents such as bortezomib (6,7), thalidomide (8,9), and rituximab (10); radiation therapy of radio-sensitive solid tumors (11); and total-body irradiation (12).

### Definitions: The Cairo-Bishop Criteria

Although no classification scheme for TLS is uniformly accepted, that of Cairo and Bishop is often used (13). The lack of universal definitions for diagnosis has made the analysis of studies examining TLS as an exposure or outcome complicated because of heterogeneity. The Cairo-Bishop definitions of “laboratory TLS” and “clinical TLS” are shown in Table 1. Clinical TLS requires the presence of laboratory TLS in addition to evidence of renal, cardiac, or neurologic dysfunction. The Cairo-Bishop classification requires an increase in electrolyte markers to occur between 3 days before and 7 days after initiation of chemotherapy, with two markers being abnormal

within a 24-hour period. This complicated time limitation requires defining TLS according to a future event (the administration of chemotherapy) and does not provide a framework for the diagnosis of spontaneous TLS (14). These definitions continue to be debated (2). From a nephrologic perspective, defining AKI on the basis of a creatinine value  $>1.5$  times the upper limit of normal for patient age and sex is not typical and does not clearly distinguish CKD from AKI. It would seem appropriate to redefine the renal criteria for clinical TLS to an absolute 0.3-mg/dl increase or relative 50% increase in creatinine over established baseline to be more closely aligned with commonly used AKI criteria (15). This more sensitive definition would potentially identify patients with TLS earlier, allowing for more rapid intervention and perhaps improved outcomes. Use of urinary and serum biomarkers may in the future allow diagnosis and treatment of very early TLS-associated AKI but has not yet been studied.

### Pathophysiology

The clinical and laboratory complications of TLS are due to release of intracellular contents into the extracellular space, overwhelming homeostatic mechanisms. Although the electrolyte complications have significant morbid potential, the liberation of nucleic acids plays a major role in the AKI seen in TLS (16).

### Uric Acid

Following the release of intracellular nucleic acids, adenine and guanine are metabolized to xanthine, which is broken down by xanthine oxidase to uric acid. This process and the relative solubilities of the molecules involved are displayed in Figure 1. In most animals, uric acid is metabolized to the highly soluble allantoin by urate oxidase. Humans and many other

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**Table 1. Cairo-Bishop classification of tumor lysis syndrome in adults**

Laboratory TLS	Clinical TLS
Uric acid: $\geq 8.0$ mg/dl	AKI (defined as creatinine $>1.5\times$ the upper limit of normal for patient age and sex)
Potassium: $\geq 6.0$ mEq/dl	Cardiac arrhythmia
Phosphorus: $\geq 4.6$ mg/dl	Seizure, tetany, or other symptomatic hypocalcemia
Calcium: $\leq 7.0$ mg/dl	

Patients must meet more than two of four laboratory criteria in the same 24-hour period within 3 days before to 7 days after chemotherapy initiation. A  $>25\%$  increase from “baseline” laboratory values is also acceptable (13). Other causes of AKI (e.g., nephrotoxin exposure, obstruction) should be excluded. TLS, tumor lysis syndrome.

primates lack this enzyme, making less soluble uric acid the final end product of adenine and guanine metabolism.

Uric acid impairs kidney function *via* crystal-dependent and crystal-independent mechanisms, with crystal-dependent processes generally considered to be more important (17). An acid urine pH favors production of poorly soluble uric acid over the more soluble urate, increasing the risk for precipitation of intratubular uric acid crystals. Conger and Falk evaluated uric acid nephropathy in a rat model, demonstrating marked increases in proximal and distal tubular pressures in rats given exogenous uric acid loads along with a uricase inhibitor (18). In addition, peritubular capillary pressures were increased two-fold, and vascular

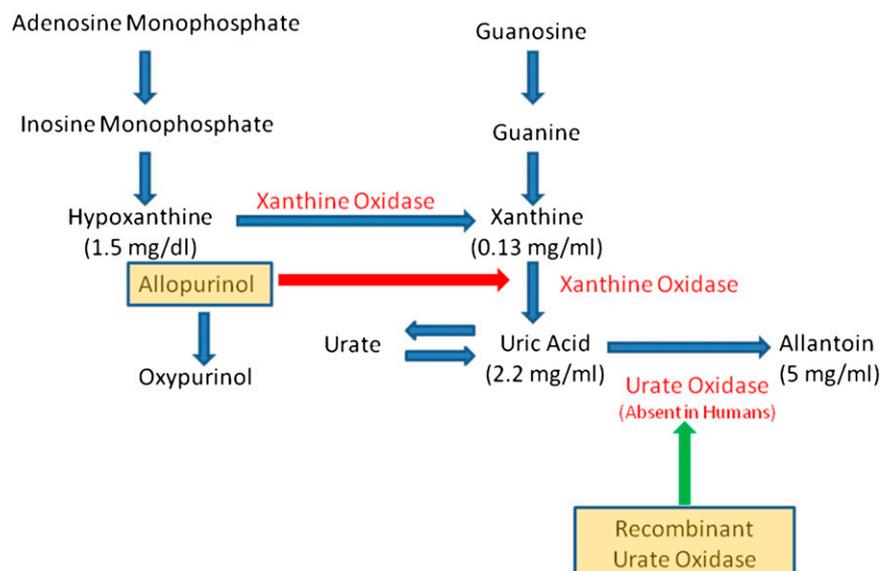
resistance beyond the peritubular capillaries was increased by more than three-fold. These findings demonstrated that acute uric acid nephropathy is related not only to tubular obstruction but also to marked hemodynamic changes in multiple renal vessels. Even at soluble concentrations, uric acid may predispose to renal ischemia. Uric acid can scavenge bioavailable nitric oxide, leading to vasoconstriction (19). Vascular smooth muscle cells exposed to dissolved uric acid release the inflammatory cytokines monocyte chemoattractant protein-1, TNF- $\alpha$ , and other vasoactive mediators, leading to chemotaxis of white cells and further inflammatory injury (20). Finally, uric acid may inhibit proximal tubule cell proliferation, prolonging the duration of kidney injury (21).

**Potassium**

The intracellular concentration of potassium is as high 120 mEq/L (22,23). In the case of hematologic malignancies, much of the 2.6 kg of bone marrow in the average human may be replaced by malignant cells. The rapid liberation of potassium into the extracellular fluid will lead to severe hyperkalemia if it exceeds the normal homeostatic uptake of potassium into liver and muscle cells. In the setting of CKD or AKI, renal clearance of potassium is reduced, increasing the severity of hyperkalemia (24). Hyperkalemia can lead to weakness and death *via* cardiac arrhythmia.

**Phosphorous and Calcium**

TLS can rapidly liberate a large volume of intracellular phosphate. Hyperphosphatemia is less common in cases of spontaneous TLS than in typical TLS, presumably because of the rapid uptake of extracellular phosphate by the remaining highly active residual tumor cells in the former condition (25–28). Hyperphosphatemia in patients with TLS will be further exacerbated by any associated AKI.



The primary toxicity of hyperphosphatemia is the secondary hypocalcemia that results from chelation of calcium by phosphate anions. Hypocalcemia can lead to cardiac arrhythmias, seizures, tetany, and death. Interestingly, prolonged hypocalcemia has been described even after resolution of hyperphosphatemia in TLS, presumably due to a deficiency of 1,25-vitamin D (29).

The precipitation of calcium-phosphate crystals within the renal parenchyma, nephrocalcinosis, may also play a significant role in the decreased GFR seen in this condition (30,31). The observation that TLS can cause AKI even in animals that are able to metabolize uric acid to allantoin points to a potentially important role for hyperphosphatemia in the pathogenesis of TLS-associated AKI (32).

### Epidemiology

The incidence of TLS varies widely, ranging from sporadic case reports in certain solid malignancies to the 26.4% incidence described in high-grade B-cell acute lymphoblastic leukemia (33). Table 2 describes relative risk for TLS in various hematologic and nonhematologic malignancies. The highest risk for TLS is seen in large-volume, highly metabolic malignancies, such as B-cell acute lymphoblastic leukemia and Burkitt 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 (34). Spontaneous TLS is typically observed in high-grade hematologic malignancies.

### TLS in Solid Tumors

The true incidence of TLS in solid malignancies is not well defined, perhaps because of a lack of significant surveillance for this complication of treatment. Case reports exist across a variety of solid tumors, however, including small-cell carcinoma, germ-cell tumors, neuroblastoma,

medulloblastoma, hepatoblastoma, breast carcinoma, non-small-cell lung cancer, vulvar carcinoma, thymoma, ovarian carcinoma, colorectal carcinoma, gastric carcinoma, melanoma, hepatocellular carcinoma, and sarcoma (35). Although a recommendation to include routine measurement of serum uric acid, potassium, calcium, or phosphorus during treatment of solid malignancies would be premature, nephrologists should certainly consider this syndrome in any differential diagnosis of AKI in a patient with a solid malignancy.

### Identification of Individuals at Risk

In addition to type of malignancy, several other risk factors for the development of TLS have been identified. A study at our institution retrospectively examined 194 patients with acute myeloid leukemia, of whom 19 developed clinical or laboratory TLS. In univariate analysis, a strong association was demonstrated between baseline creatinine level and the development of TLS {odds ratio (OR), 31.2 (95% confidence interval [CI], 6.1–160.0); per mg/dl creatinine}. Other predictors included pretreatment uric acid level (OR, 30.16 [95% CI, 6.12–148.63]), lactate dehydrogenase (OR, 2.9 [95% CI, 1.6–5.2]), and male sex (OR, 4.8 [95% CI, 1.5–15.0]) (36). Similar results have been seen across a variety of tumor types (33,37–39). Table 3 summarizes these additional risks.

### Effect of Kidney Function

A reduced GFR compromises the ability to excrete excess solutes, potentially leading to elevated serum levels of phosphorus and uric acid, which may further compromise renal function. The association between renal function and development of TLS is strong and has been seen across a variety of populations and tumor subtypes. A prospective study of 1192 patients with non-Hodgkin lymphoma (of whom 63 developed TLS) revealed pre-existing renal dysfunction in 68% of those affected; however,

**Table 2. Incidence of tumor lysis syndrome in various malignancies**

Malignancy (Reference)	Incidence (%)	Risk
<b>Hematologic</b>		
Burkitt lymphoma (33)	14.9	High
B cell ALL (33)	26.4	High
diffuse large-B cell lymphoma (87)	6	Intermediate
ALL	5.2–23	May vary by WBC count, with >100,000 cells/mm <sup>3</sup> being highest risk
AML: WBC count >75,000 cells/mm <sup>3</sup> (37)	18	High
AML: WBC count 25,000–75,000 cells/mm <sup>3</sup> (37)	6	Intermediate
AML: WBC count <25,000 cells/mm <sup>3</sup> (37)	1	Low
chronic lymphocytic leukemia (88)	0.33	Low (higher with WBC >100,000 cells/mm <sup>3</sup> )
chronic myeloid leukemia (89)	Case reports only	Low
multiple myeloma (90)	1	Low
<b>Nonhematologic</b>		
solid tumors (35)	Unknown	Low

Many studies do not differentiate between laboratory and clinical tumor lysis syndrome. Risk category as per Cairo *et al.* (51). ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; WBC, white blood cell.

**Table 3. Predictors of tumor lysis syndrome**

Characteristic	Risk Factor
Tumor burden	Bulky lymphatic disease (>10 cm) Elevated lactate dehydrogenase (2× upper limit of normal) Elevated white blood cell count (>25,000 cells/mm <sup>3</sup> )
Renal function	Baseline creatinine > 1.4 mg/dl (37)
Baseline uric acid	>7.5 mg/dl
Chemosensitivity	Variable

Adapted from reference 91.

ruling out antecedent low-grade TLS was not possible in this population (40). Among a group of 772 patients with a new diagnosis of acute myeloid leukemia, pretreatment creatinine concentration was strongly predictive of the development of clinical and laboratory TLS. Patients with pretreatment creatinine concentrations >1.4 mg/dl had 10.7 times the odds of developing TLS (95% CI, 4.5–25.1) compared with those under that threshold (37). Further studies using estimated GFR rather than creatinine concentration will help to better elucidate differences in risk among varying degrees of kidney function while minimizing potential confounding by sex and race.

**Value of Urine Uric Acid-to-Creatinine Ratio**

Kelton *et al.* documented an increased spot urine uric acid-to-creatinine ratio in 5 patients with acute uric acid nephropathy versus 27 patients with AKI from other causes. A cutoff of 1.0 was reported to be 100% sensitive and specific in this small study (41). However, a subsequent study examining the use of urine uric acid-to-creatinine ratio in non-malignancy-associated AKI demonstrated elevations >1.0 g/g in 12 of 23 patients (42). Thus, testing of urine uric acid and calculation of the urine uric acid-to-creatinine ratio to predict the risk for or confirm the presence of TLS is not recommended.

**Mortality**

TLS is associated with higher tumor burden but also with therapeutic efficacy, making inferences about TLS-specific mortality difficult. The presence of AKI, even after adjustment for other markers of severity of illness, seems to be a potent predictor of death in TLS (43). A recent retrospective study of 63 patients with hematologic malignancies and TLS demonstrated a 6-month mortality rate of 21% in

the group without AKI and 66% in the group with AKI (44). This relationship persisted after multivariable adjustment, with AKI independently increasing the odds of 6-month mortality by 5.61 (95% CI, 1.64–54.66). Preventing AKI should be a primary therapeutic aim in patients at risk for TLS.

**Prophylaxis and Treatment**

Goals of TLS therapy address the pathophysiologic derangements discussed in the preceding section. Thus, therapy should be directed at increasing clearance of toxic intracellular contents. The choice of prophylactic therapy depends on the risk for TLS given specific patient and disease characteristics (Table 4). We provide our algorithmic approach to prophylaxis and therapy in Figure 2. In addition to specific therapies discussed in the following section, care should be taken also to avoid potentially nephrotoxic substances, including intravenous contrast and nonsteroidal anti-inflammatory agents, in patients at risk for TLS. Discontinuation of angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers is also probably appropriate in patients with TLS and AKI.

**Volume Expansion**

Fluid resuscitation is a mainstay of therapy in TLS (45,46) and is recommended as prophylaxis in any patient at risk of developing the syndrome (47). Crystalloid volume expansion increases renal clearance of potassium, phosphate, and uric acid. In addition, distal delivery of sodium and chloride augment potassium secretion. Increased urine flow in the setting of volume expansion decreases both the calcium-phosphate product in the urine as well as the urine concentration of uric acid, potentially reducing obstructive crystal formation. Current consensus statements suggest fluid intake targets of 3 L/d using intravenous or oral therapy before the start of chemotherapy, provided pre-existing volume overload or oliguric AKI is not present (48).

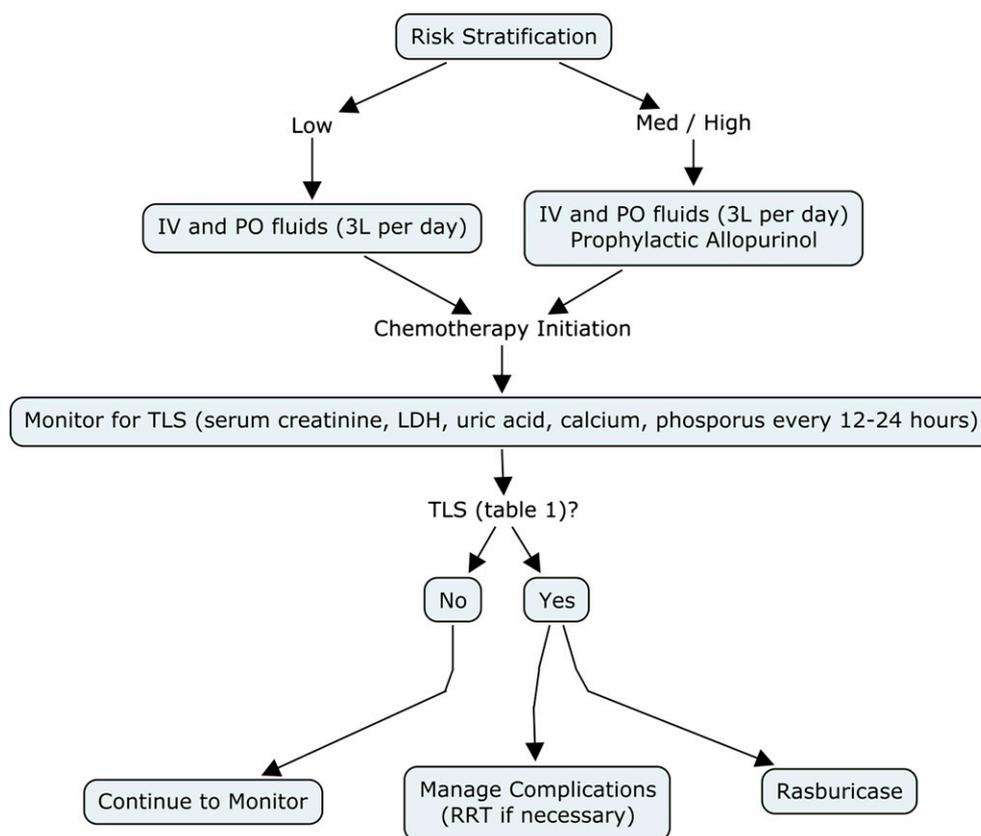
**Diuretics**

Insofar as diuretics enhance urinary flow, one would expect decreased nephrotoxicity from urinary precipitation of uric acid or calcium-phosphate crystals. That said, the cytokine-mediated hemodynamic compromise seen in TLS may be adversely affected by excessive volume depletion due to diuretics (49). Because diuretics do not have a proven role in reducing the incidence or severity of TLS, their routine use is not recommended unless there are clinical signs or symptoms of volume overload.

**Table 4. Consensus recommendations for prophylaxis of tumor lysis syndrome (51)**

Tumor Lysis Syndrome Risk	Monitoring	Volume Expansion	Allopurinol	Rasburicase
Low	X	X		
Medium	X	X	X	
High	X	X	X	X <sup>a</sup>

<sup>a</sup>Contraindicated in patients with glucose-6-phosphate dehydrogenase deficiency.



**Figure 2.** | Algorithmic approach to prophylaxis and treatment of tumor lysis syndrome (TLS). IV, intravenous; LDH, lactate dehydrogenase; PO, oral; RRT, renal replacement therapy.

### Urinary Alkalinization

Alkalinization of the urine favors conversion of uric acid to the more soluble urate salt, decreasing the potential for intra-tubular crystal formation. The solubility of urate in urine with a pH of 7 is 2.2 mg/ml, while that of uric acid in urine with a pH of 5 is only 0.15 mg/ml. However, animal studies did not demonstrate a reduction in urate nephropathy with urine alkalinization compared with saline administration (18), and no controlled human studies exist to inform the decision of whether to attempt alkalinization. In addition, administering exogenous alkali decreases the solubility of calcium-phosphate salts, leading to increased soft-tissue and renal tubular deposition of calcium-phosphate crystals. Further, alkalemia favors calcium binding to albumin, decreasing ionized calcium concentration, which may precipitate tetany or arrhythmia in these patients who are already prone to hypocalcemia. Finally, in the era of recombinant urate oxidase treatment (see later discussion) the benefit of increased solubility of uric acid resulting from urinary alkalinization is probably largely attenuated. Therefore, urinary alkalinization for the prevention or treatment of TLS is not generally recommended and may be harmful.

### Allopurinol

Allopurinol is a purine analogue and structural isomer of hypoxanthine. It is metabolized by xanthine oxidase to oxypurinol, its active form, which is a competitive xanthine

oxidase inhibitor. Oxypurinol is excreted by the kidneys with a long half-life of up to 24 hours in normal individuals, making dosing complex in patients with CKD or AKI. Allopurinol decreases the generation of uric acid from xanthine but does not have a direct effect on uric acid levels (50). As such, initiation of allopurinol therapy after marked hyperuricemia has already occurred and TLS has progressed significantly is unlikely to alter the clinical course, and treatment with rasburicase, discussed later, may be more appropriate. However, prophylactic use of allopurinol is generally recommended in patients with high- or intermediate-risk tumors (51).

Allopurinol is associated with several potentially severe adverse effects, including Stevens-Johnson syndrome, toxic epidermal necrolysis, hepatitis, bone marrow suppression, and the allopurinol hypersensitivity syndrome (a highly morbid condition consisting of rash, acute hepatitis, and eosinophilia) (52). There has been concern that the renal excretion of allopurinol predisposes patients with CKD or AKI to these adverse reactions, although it is unclear whether these reactions are dose-related, or even whether the allergen is allopurinol or its metabolite oxypurinol. Thus, there may be a tendency to “underdose” allopurinol in an effort to reduce adverse events. A cohort study of 120 patients, some of whom received allopurinol with dosing adjusted for their reduced GFR while others received standard dosing, showed no increase in the rate of toxic reactions in the standard dosing group (53). A case-control

study examining risk factors for allopurinol hypersensitivity syndrome did not find an association between allopurinol dose and the development of this syndrome, although case-patients had a higher prevalence of CKD (55% versus 21%;  $P < 0.001$ ) (54). Skin testing and lymphocyte culture methods have proven unsuccessful at predicting which patients will develop these severe complications (53). Because the preponderance of evidence suggests that these reactions are not dose-related, allopurinol dosing should be guided by the uric acid level and TLS risk.

Treatment with allopurinol also increases plasma concentrations of the uric acid precursors hypoxanthine and xanthine, which themselves inhibit enzymes involved in purine synthesis. Poorly soluble, xanthine has been demonstrated to lead to decreases in GFR due to precipitation of crystals in renal tubules and stone formation (55,56). Xanthine crystalluria or stone formation may thus be exacerbated or triggered by the administration of allopurinol.

**Febuxostat**

Febuxostat, a novel xanthine oxidase inhibitor that does not have the hypersensitivity profile of allopurinol and does not require dosing adjustments for reduced GFR, is an attractive consideration for prophylaxis in patients at risk for TLS with impaired kidney function. However, there are no active or completed clinical trials evaluating the use of febuxostat for this indication (57). Febuxostat does seem to be efficacious in the treatment of hyperuricemia associated with gout (58,59). Because its mechanism of action is similar to that of allopurinol, febuxostat would not be expected to decrease the accumulation of xanthine or the risk for xanthine stone formation. Febuxostat may be a reasonable, albeit expensive, alternative to allopurinol in the prophylaxis of TLS in patients with decreased estimated GFR, especially if there is any history of allergy or other adverse reactions to allopurinol.

**Recombinant Urate Oxidase**

Rasburicase is a recombinant form of *Aspergillus*-derived urate oxidase expressed in a *Saccharomyces cerevisiae* vector. As discussed earlier, urate oxidase, although present in many mammalian species, is not present in humans. Urate oxidase metabolizes uric acid to the much more soluble allantoin, carbon dioxide, and hydrogen peroxide. The former is readily excreted by the kidneys. The liberation of hydrogen peroxide can be devastating in patients with glucose-6-phosphate dehydrogenase deficiency, in whom the unchecked oxidative potential of H<sub>2</sub>O<sub>2</sub> can lead to methemoglobinemia and hemolytic anemia (60). Rasburicase will continue to be active in blood samples *ex vivo*, and thus inappropriately handled laboratory specimens may manifest spuriously low uric acid levels. Samples for uric acid should be placed on ice immediately after phlebotomy and run as quickly as possible to maximize reliable approximation of *in vivo* uric acid concentration.

Rasburicase is indicated for a single course of treatment for the initial management of elevated uric acid levels in pediatric and adult patients with leukemia, lymphoma, and solid tumor malignancies who are receiving anticancer therapy expected to result in TLS. Few randomized trials exist to inform the use of this agent (Table 5). Only three randomized, controlled trials have been published. In each

Study	Year	Patients (n)	Population	Group 1	Group 2	End Point	Superior Group
Cortes <i>et al.</i> (61) <sup>a</sup>	2010	183	Adults at risk for TLS	Rasburicase, 0.20 mg/kg per d for 5 d	Allopurinol, 300 mg/d for 5 d	Uric acid <7.5 mg/dl at 3–7 d	1
Malaguamera <i>et al.</i> (68)	2009	38	Hyperuricemic elderly patients	Rasburicase, 4.5 mg for 1 dose	Placebo	Change in uric acid at 1 wk	1
Kikuchi <i>et al.</i> (92)	2009	30	Japanese children at risk for TLS	Rasburicase, 0.20 mg/kg per d for 5 d	Rasburicase, 0.15 mg/kg per d for 5 d	Sustained reduction in uric acid to <6.5 mg/dl (age <13 yr) or <7.5 mg/dl (age ≥13 yr)	1
Ishizawa <i>et al.</i> (93)	2009	50	Japanese adults at risk for TLS	Rasburicase, 0.20 mg/kg per d for 5 d	Rasburicase, 0.15 mg/kg per d for 5 d	Sustained reduction of uric acid <7.5 mg/dl	Equivalent
Goldman <i>et al.</i> (77)	2001	52	Children at risk for TLS	Rasburicase, 0.20 mg/kg per d for 5–7 d	Allopurinol, 300 mg every 8 h for 5–7 d	Area under the uric acid curve over 5 d	1

TLS, tumor lysis syndrome.

<sup>a</sup>Study also contained a rasburicase and sequential allopurinol group (n = 92).

of these cases, the primary endpoint was based on a reduction of serum uric acid concentration at a specified time point. No studies were powered to demonstrate a morbidity (e.g. AKI, need for dialysis) or mortality benefit of this agent versus standard therapy.

The efficacy of rasburicase as a uric acid–lowering agent is undeniable, and it seems to be extremely well tolerated, with adverse events occurring in less than 5% of patients in the largest adult trial (61). These reactions were generally mild, allergic-type responses, with a severe (grade 4) hypersensitivity reaction occurring in a single patient. Testing for glucose-6-phosphate dehydrogenase deficiency is recommended in all patients at risk for this condition before the administration of rasburicase.

The acquisition wholesale price for rasburicase in the United States is currently approximately \$3600 for a 7.5-mg vial. Recommended dosing is 0.15–0.20 mg/kg per day for a total of 5 days, according to the package insert. The total treatment cost for a 75-kg individual would thus be approximately \$36,000. An expert panel convened in 2010, sponsored by the manufacturer of rasburicase (Sanofi-Aventis), recommended the prophylactic use of rasburicase in adults with a high-risk malignancy, with other patients receiving rasburicase after chemotherapy in the setting of elevated uric acid levels (51). Several cohort studies have demonstrated persistently suppressed serum uric acid concentrations with one-time dosing; a dose of 0.15 mg/kg seems to be a clinically reasonable and cost-effective approach (62–74). Repeat dosing may be needed if uric acid remains at or increases above 8.0 mg/dl after the initial dose (75).

Antirasburicase antibody formation was documented in 17 of 121 (14%) of patients receiving rasburicase in one clinical trial; these antibodies were not correlated with any specific adverse events (76). A smaller trial in children with hematologic malignancies did not detect any such antibodies (77). The presence of antibodies raises concern for subsequent hypersensitivity reactions or, in the case of neutralizing antibody, decreased efficacy of rasburicase with repeated dosing. That said, TLS is most common on the initial presentation of disease because relapsed malignancies tend to be more chemotherapy-resistant, thereby decreasing the risk for recurrent TLS. An ongoing clinical trial has been designed to elucidate the issue of antibody formation with rasburicase therapy in greater detail (ClinicalTrials.gov record NCT01097369).

A 2010 Cochrane review examined five controlled clinical trials of the use of urate oxidase (rasburicase and uricozyme) in the prevention and treatment of TLS in children (78). Despite excellent evidence of a reduction in serum uric acid concentration, no benefits in terms of prevention of AKI or mortality were demonstrated. The authors concluded that clinicians should weigh the risks and benefits of urate oxidase treatment in patients with hematologic malignancies.

In summary, rasburicase is increasingly used to treat TLS once established in patients meeting laboratory criteria for TLS. Subsequent dosing should be based on clinical course, presence or absence of AKI, and measurement of follow-up uric acid levels, with careful attention to proper collection techniques.

Pegloticase is a more recently approved pegylated mammalian recombinant uricase produced by a genetically

modified strain of *Escherichia coli* that is approved in the United States for treatment of chronic treatment-resistant gout (79). It is not approved for treatment of TLS, and its use in this setting has not been reported. Its contraindications (glucose-6-phosphate dehydrogenase deficiency) and warnings are similar to those of rasburicase.

### Exogenous Calcium

The administration of calcium to patients with hypocalcemia as a consequence of TLS can be expected to increase calcium-phosphate deposition in soft tissues, potentially worsening AKI with its attendant morbidity and mortality. Therefore, administration of exogenous calcium should be reserved for patients with severe hypocalcemia and clinical manifestations, such as tetany, electrocardiographic changes, or cardiac arrhythmia.

### Dialytic Modalities

The goal of dialytic therapy in TLS is to augment the clearance of potassium, phosphate, and uric acid; correct any significant metabolic acidosis and disorders of serum calcium concentration; and provide appropriate therapy for associated AKI. Given the potential ongoing liberation of these substances from lysing cells, continuous therapies are often preferred. That said, hemodialysis, with the attendant rapid clearance of potassium, may be the modality of choice for life-threatening hyperkalemia; this can then be followed by a continuous therapy at high dialysate or replacement fluid flow rates (of 3–4 L/h) to avoid rebound hyperkalemia and provide ongoing dialytic therapy for TLS (80).

Phosphate clearance with dialysis is time dependent, making it difficult to achieve adequate phosphate removal with intermittent hemodialysis as typically performed in the hospital. Continuous renal replacement therapy, such as continuous veno-venous hemofiltration, continuous veno-venous hemodialysis, or combination therapy, may be preferable in the setting of severe hyperphosphatemia. High dialysate flow rate (3–4 L/h) may be necessary to adequately maintain clearance in the face of active liberation of cellular contents (80–82). Because acute peritoneal dialysis achieves inadequate uric acid clearance, its routine use is not recommended in TLS (83). Continuous therapies may be combined with hemodialysis to affect the rapid clearance of a solute (*via* hemodialysis) with its sustained suppression (continuous therapy) (84). Prophylactic continuous renal replacement therapy has been studied in children and adults at risk for TLS (85,86), but its role in the prevention of AKI and metabolic consequences of TLS has yet to be defined; thus, it is not recommended at this time.

### Summary

TLS dramatically increases mortality and is frequently seen in certain hematologic malignancies and, rarely, in a wide variety of other malignant diseases. It is characterized by the failure of usual homeostatic mechanisms to adequately re-sequester or excrete nucleic acid, potassium, and phosphorus liberated from rapidly lysing tumor cells and can lead to renal failure, tetany, cardiac arrhythmia, seizure, and death. All patients at risk for the syndrome should receive judicious volume repletion and allopurinol

before initiation of chemotherapy, with frequent laboratory assessments after chemotherapy begins. Rasburicase, a novel recombinant urate oxidase, may play a valuable (if expensive) role in higher-risk patients. If dialysis is required, continuous modalities may be favored, particularly in patients with more severe TLS.

#### Disclosures

None.

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