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.

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); 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
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 chemotactic protein-1, TNF-α, 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 as 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.

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

<table>
<thead>
<tr>
<th>Laboratory TLS</th>
<th>Clinical TLS</th>
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</thead>
<tbody>
<tr>
<td>Uric acid: ≥8.0 mg/dl</td>
<td>AKI (defined as creatinine &gt;1.5× the upper limit of normal for patient age and sex)</td>
</tr>
<tr>
<td>Potassium: ≥6.0 mEq/dl</td>
<td>Cardiac arrhythmia</td>
</tr>
<tr>
<td>Phosphorus: ≥4.6 mg/dl</td>
<td>Seizure, tetany, or other symptoms</td>
</tr>
<tr>
<td>Calcium: ≤7.0 mg/dl</td>
<td>Symptomatic hypocalcemia</td>
</tr>
</tbody>
</table>

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.

Figure 1. Metabolism of purine nucleic acids. In humans and apes, the end product is uric acid. Allopurinol inhibits metabolism of xanthine to uric acid. Recombinant urate oxidase catalyzes the metabolism of uric acid into the more soluble allantoin (55,94,95). Solubilities at a pH of 7 are shown in parentheses.
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, 6.1–148.63]), 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 preexisting renal dysfunction in 68% of those affected; however,

<table>
<thead>
<tr>
<th>Table 2. Incidence of tumor lysis syndrome in various malignancies</th>
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<tbody>
<tr>
<td><strong>Malignancy (Reference)</strong></td>
</tr>
<tr>
<td>-----------------------------</td>
</tr>
<tr>
<td>Hematologic</td>
</tr>
<tr>
<td>Burkitt lymphoma (33)</td>
</tr>
<tr>
<td>B cell ALL (33)</td>
</tr>
<tr>
<td>diffuse large-B cell lymphoma (87)</td>
</tr>
<tr>
<td>ALL</td>
</tr>
<tr>
<td>AML: WBC count &gt;75,000 cells/mm³ (37)</td>
</tr>
<tr>
<td>AML: WBC count 25,000–75,000 cells/mm³ (37)</td>
</tr>
<tr>
<td>AML: WBC count &lt;25,000 cells/mm³ (37)</td>
</tr>
<tr>
<td>chronic lymphocytic leukemia (88)</td>
</tr>
<tr>
<td>chronic myeloid leukemia (89)</td>
</tr>
<tr>
<td>multiple myeloma (90)</td>
</tr>
<tr>
<td>Nonhematologic</td>
</tr>
<tr>
<td>solid tumors (35)</td>
</tr>
</tbody>
</table>

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.
Mortality

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 \(>1.4 \text{ mg/dl} \) 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 \(>1.0 \text{ g/g} \) 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.

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 3. Predictors of tumor lysis syndrome**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Risk Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor burden</td>
<td>Bulky lymphatic disease (&gt;10 cm)</td>
</tr>
<tr>
<td></td>
<td>Elevated lactate dehydrogenase</td>
</tr>
<tr>
<td></td>
<td>(2\times) upper limit of normal</td>
</tr>
<tr>
<td></td>
<td>Elevated white blood cell count</td>
</tr>
<tr>
<td></td>
<td>(&gt;25,000 cells/mm(^3))</td>
</tr>
<tr>
<td>Renal function</td>
<td>Baseline creatinine (&gt;1.4 \text{ mg/dl}) (37)</td>
</tr>
<tr>
<td>Baseline uric acid</td>
<td>(&gt;7.5 \text{ mg/dl})</td>
</tr>
<tr>
<td>Chemosensitivity</td>
<td>Variable</td>
</tr>
</tbody>
</table>

Adapted from reference 91.

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

<table>
<thead>
<tr>
<th>Tumor Lysis Syndrome Risk</th>
<th>Monitoring</th>
<th>Volume Expansion</th>
<th>Allopurinol</th>
<th>Rasburicase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Medium</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X(^a)</td>
</tr>
</tbody>
</table>

\(^a\)Contraindicated in patients with glucose-6-phosphate dehydrogenase deficiency.
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.

Feboxostat

Feboxostat, 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 feboxostat for this indication (57). Feboxostat 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, feboxostat would not be expected to decrease the accumulation of xanthine or the risk for xanthine stone formation. Feboxostat 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 \( \text{H}_2\text{O}_2 \) can lead to methemoglobinemia and hemolytic anemia (60). Rasburicase will continue to be active in blood samples \textit{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 \textit{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

<table>
<thead>
<tr>
<th>Year</th>
<th>Patients (n)</th>
<th>Population</th>
<th>Group 1</th>
<th>Group 2</th>
<th>End Point</th>
<th>Superior Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010</td>
<td>183</td>
<td>Adults at risk for TLS</td>
<td>Rasburicase, 0.20 mg/kg per d for 5 d</td>
<td>Allopurinol, 300 mg/d for 5 d</td>
<td>Uric acid &lt;7.5 mg/dl at 3–7 d</td>
<td>1</td>
</tr>
<tr>
<td>2009</td>
<td>38</td>
<td>Hyperuricemic elderly patients at risk for TLS</td>
<td>Rasburicase, 4.5 mg for 1 dose</td>
<td>Placebo</td>
<td>Change in uric acid at 1 wk</td>
<td>1</td>
</tr>
<tr>
<td>2010</td>
<td>183</td>
<td>Japanese children at risk for TLS</td>
<td>Rasburicase, 0.20 mg/kg per d for 5 d</td>
<td>Rasburicase, 0.15 mg/kg per d for 5 d</td>
<td>Sustained reduction in uric acid to &lt;6.5 mg/dl (age &lt;13 yr) or &lt;7.5 mg/dl (age ≥13 yr)</td>
<td>1</td>
</tr>
<tr>
<td>2009</td>
<td>50</td>
<td>Japanese adults at risk for TLS</td>
<td>Rasburicase, 0.15 mg/kg per d for 5 d</td>
<td>Rasburicase, 0.20 mg/kg per d for 5 d</td>
<td>Sustained reduction of uric acid, 7.5 mg/dl</td>
<td>Equivalent</td>
</tr>
<tr>
<td>2001</td>
<td>52</td>
<td>Children at risk for TLS</td>
<td>Rasburicase, 0.20 mg/kg per d for 5–7 d</td>
<td>Allopurinol, 300 mg every 8–12 h for 5–7 d</td>
<td>Area under the uric acid curve over 5 d</td>
<td>1</td>
</tr>
</tbody>
</table>
of these cases, the primary endpoint was based on a reduc-
tion of serum uric acid concentration at a specified time 
point. No studies were powered to demonstrate a morbid-
ity (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 gener-
ally 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 ap-
proach (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 antibod-
ies (77). The presence of antibodies raises concern for sub-
sequent 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 malig-
nancies 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 forma-
tion 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). De-
spite 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 ox-
dase 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 mammal-
man 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 contraindica-
tions (glucose-6-phosphate dehydrogenase deficiency) and 
warnings are similar to those of rasburicase.

Exogenous Calcium

The administration of calcium to patients with hypocal-
cemia 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 atten-
dant 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 re-
placement 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 pref-
erable in the setting of severe hyperphosphatemia. High 
dialysate flow rate (3–4 L/h) may be necessary to ade-
quately maintain clearance in the face of active liberation 
of cellular contents (80–82). Because acute peritoneal dial-
ysis 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 clear-
ance of a solute (via hemodialysis) with its sustained suppres-
sion (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 ade-
quately 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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37. Montesinos P, Lorenzo I, Martínez D, Ortí G, Algarra L, Martínez J, Moscardo’ F, de la Rubia JM e d


Published online ahead of print. Publication date available at www.cjasn.org.