How We Treat Tumor Lysis Syndrome


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When tumor cells are rapidly broken down and their contents released into the extracellular space, the released ions and compounds can cause metabolic disturbances too great to be neutralized by the body's normal mechanisms. The syndrome characterized by these metabolic derangements is known as tumor lysis syndrome (TLS). TLS can cause life-threatening conditions and even death unless appropriately and immediately treated.

Risk Factors

There are many factors that predispose a patient to TLS. Those at greatest risk are patients with large tumor burdens (bulky disease) that proliferate at a high rate, and those with renal insufficiency or dehydration prior to the start of therapy. Hyperuricemia, hyperphosphatemia, and an elevated lactate dehydrogenase (LDH) level prior to the start of therapy for the malignancy also correlate with a risk of TLS developing.[1,2]

Certain malignancies may also predispose a patient to development of this syndrome. TLS is frequently associated with treatment of Burkitt lymphoma, acute lymphoblastic leukemia, acute myeloid leukemia, and other high-grade lymphomas (Figure 1).[1-3] Post-treatment TLS has also been reported in patients with multiple myeloma, as well as in solid tumors, such as breast cancer, small-cell lung cancers, sarcoma, non-small-cell lung cancer, bladder cancer, and ovarian cancer.[4-9] The incidence of TLS in patients with solid tumors, however, is relatively low compared with that observed in hematologic malignancies. Spontaneous occurrences prior to starting therapy have also been described in leukemias and lymphomas.[2,10-12]

Certain therapies for malignancies may also place patients at risk for the development of TLS. Patients who are treated with intensive protocols are at a relatively higher risk compared with those who receive fewer chemotherapeutic agents.[13] There are case reports indicating that corticosteroids alone may be enough to induce TLS, especially if the patient has a hematologic malignancy.[14,15] In addition, treatment of chronic leukemia with adenosine deaminase inhibitors (as opposed to alkylating agents) has been reported to induce TLS and subsequent renal failure.[16] Finally, studies have shown that patients who receive therapy with monoclonal antibodies and other targeted agents may also be at a relatively higher risk for the development of TLS than those who do not receive this modality of treatment.[17,18]

Pathophysiology

TLS occurs when there is a rapid breakdown of nucleic acids and lysis of tumor cells during or in the days following chemotherapy initiation, resulting in characteristic electrolyte abnormalities. All of these abnormalities can have lethal consequences. Two of the most life-threatening complications
are arrhythmias, due to hypocalcemia or hyperkalemia, and renal failure, due to hyperuricemia or hyperphosphatemia. Hyperkalemia can result from two different mechanisms. Because the potassium gradient across cell membranes is regulated by a sodium/potassium adenosine triphosphatase (ATPase), any disruption in the functioning of this enzyme can give rise to an efflux of potassium out of the cell. When exposed to chemotherapy or radiation therapy, cellular metabolism is increased and adenosine triphosphate (ATP) is consumed at a higher rate. Consequently, there is little ATP remaining for the ATPase enzyme to use to maintain the potassium gradient. Potassium therefore leaves the malignant cells even prior to lysis.[19] The second mechanism is the release of the intracellular stores of potassium into the blood upon lysis of tumor cells. Hyperkalemia is typically seen in the first 12 to 24 hours after therapy and is therefore the initial life-threatening abnormality seen in TLS.[20,21] Hypocalcemia in this syndrome occurs secondary to hyperphosphatemia, as phosphate is released from lysed cells. Malignant hematologic cells contain up to four times more intracellular phosphate than normal lymphoid cells.[22] Thus, phosphate levels can become extremely elevated in TLS. Significant elevations in phosphorus levels are not appreciated until the levels exceed the capacity for renal phosphate excretion. This usually occurs 24 to 48 hours after the start of therapy.[21] The concomitant hypocalcemia results from the increased calcium-phosphate product and the precipitation of calcium salts into the kidney and other ectopic areas. The ensuing hypocalcemia can not only lead to tetany and seizures, but can also give rise to lethal cardiac arrhythmias. Hyperuricemia is usually seen 48 to 72 hours after the initiation of treatment.[22] Nucleic acid purines, which are released into the blood after cell lysis, are eventually catabolized to uric acid by xanthine oxidase. Under normal circumstances, purines are reused by salvage pathways in the cells so as to minimize their excretion. However, with tumor cell lysis, the salvage pathways of the remaining cells become overwhelmed and there is a large net secretion of uric acid into the renal tubules after filtration in the kidneys.[21] This can lead to renal failure, as will be discussed below.

Mechanisms and Consequences of Acute Renal Failure

There are several potential mechanisms of acute renal failure in patients with TLS. Intravascular volume depletion can create a stimulus for uric acid reabsorption and subsequent net secretion into the distal tubules.[23] The increase in urinary uric acid secretion in the presence of the acidic local environment of the kidney (pH~5.0) promotes uric acid precipitation in the renal collecting system and distal tubules and subsequent uric acid nephropathy. This results in oliguric acute renal failure. A uric acid-to-creatinine ratio greater than 1.0 is usually suggestive of renal failure secondary to urate nephropathy.[22] The hyperphosphatemia associated with TLS can also lead to renal failure, which in this case results from an elevated level of phosphate-calcium cross product. This elevated level leads in turn to calcium phosphate salt formation and precipitation in the renal tubules. Hyperphosphatemia is usually the cause of acute renal failure in TLS, a result of the fact that prophylaxis with allopurinol has decreased the incidence of severe hyperuricemia.[21] Renal vasoconstriction in TLS, although rare, results from the release of adenosine into the circulation after tumor cell lysis.[24] TLS-induced acute renal failure has many consequences that can contribute to the rapid clinical deterioration of a patient. Oliguria can lead to volume overload, hypertension, and pulmonary edema. High blood urea nitrogen (BUN) levels can be severe enough to result in pericarditis, platelet dysfunction, and impaired cellular immunity.[13] There may also be a resulting high anion gap metabolic acidosis, which can worsen the electrolyte imbalances of TLS. Intracellular uptake of potassium becomes impaired, uric acid solubility is decreased, and an extracellular shift of phosphate is promoted. Prompt and aggressive treatment of acute renal failure is vital to avoid, or at least minimize, these complications.

Diagnosis

Tumor lysis syndrome is diagnosed clinically, with the use of laboratory parameters. Most other forms of acute renal failure are associated with lower uric acid and phosphorus levels. Post-treatment tumor lysis can be distinguished from spontaneous tumor lysis by the lack of hyperphosphatemia in the latter.[25] The importance of hyperphosphatemia as a marker for TLS cannot be overemphasized. Since the advent of allopurinol, the incidence of marked hyperuricemia has declined, and hyperphosphatemia has become the principal laboratory abnormality.[26]
Cairo-Bishop Definition of Laboratory Tumor Lysis Syndrome

The Cairo-Bishop definition provided specific laboratory criteria for the diagnosis of TLS, as well as a grading system for describing the degree of severity of TLS. Laboratory TLS (Table 1) was defined as any two (or more) of the following abnormalities:

- Serum uric acid level $\geq 8$ mg/dL, or 25% increase from baseline.
- Serum potassium level $\geq 6$ mmol/L, or 25% increase from baseline.
- Serum phosphate level $\geq 6.5$ mg/dL in children and $\geq 4.5$ mg/dL in adults, or 25% increase from baseline.
- Serum calcium level $\leq 7$ mg/dL, or 25% decrease from baseline.

All these abnormalities must occur within 3 days prior to or 7 days after the start of chemotherapy.

**TABLE 2**

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<th>Cairo-Bishop Clinical Tumor Lysis Syndrome</th>
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**Definition and Grading**

Furthermore, Cairo and Bishop defined clinical TLS as laboratory TLS plus 1 or more of the following:

- Increase in serum creatinine level $\geq 1.5$ times the upper limit of normal.
- Cardiac arrhythmia/sudden death.
- Seizures.

The grading system Cairo and Bishop used to describe the severity of TLS (Table 2) was based on the degree of serum creatinine elevation, the presence of and type of cardiac arrhythmia, and finally, the presence of and severity of seizures.[27]

**Prevention**

The identification of patients at risk for TLS and determination of the degree of risk are the cornerstones of management of TLS. The importance of prevention cannot be overstated, given that spontaneous cases of TLS with subsequent acute renal failure have been reported in patients with lymphoma and leukemia. Identifying any risk factors a patient may have is a logical first step. Correction of renal failure and/or electrolyte abnormalities prior to the initiation of chemotherapy or radiation therapy may prevent the onset of TLS, or at the very least, may decrease its subsequent intensity.

**Aggressive hydration**

Aggressive intravenous hydration at a rate of 2 to 3 L/day, maintaining a urine output of 100 to 200 mL/hour, is of paramount importance to decreasing the likelihood of uric acid and/or calcium phosphate deposition in renal tissue or tubules. Some authorities even advocate this step as a primary preventive measure, since it may be the key mechanism for protecting against acute urate nephropathy.[28] Diuretics can be used to maintain urine output if necessary, but only after correcting any volume depletion. However, diuretics are rarely needed in patients with normal renal and cardiac function. Once a patient is adequately hydrated, input should equal output; exact and frequent measurements of input and output are essential.

**Allopurinol**

Allopurinol administered prior to the onset of anti-tumor therapy has reduced, although it has not eliminated, the incidence of acute renal failure secondary to urate nephropathy in this syndrome. Allopurinol is usually given orally at a dose of 100 mg/m$^2$ every 8 hours (maximum dose, 800 mg/day) at least 1 to 2 days prior to the start of therapy and continued for up to 3 to 7 days until there is normalization of the serum uric acid level; this dose should be reduced by 50% in a patient...
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with renal failure. If oral intake is not possible, an intravenous formulation of allopurinol has been
approved for prophylaxis.[27] In a study by Smalley et al, among the adult patients who received
allopurinol for prophylaxis, prevention of hyperuricemia was seen in 93%.[27] However, even with
allopurinol prophylaxis prior to the start of chemotherapy, elevations in uric acid levels can still be
seen.[1]

Urate oxidase (rasburicase)

Certain formulations of urate oxidase, or uricase, have also been shown to be effective in the
prevention of TLS. Uricase degrades uric acid by oxidizing it to the more soluble compound called
allantoin. Uricase enzyme is found in most mammals, but not in humans.[28] The parenteral
administration of non-recombinant uricase in humans has been shown to cause allergic reactions
and even anaphylaxis. To minimize these immunologic risks, the cloning of the gene encoding urate
oxidase in Aspergillus flavus was used to develop recombinant urate oxidase, or rasburicase
(Elitek). The role of rasburicase in prophylaxis has been demonstrated in several studies, in which
good efficacy has been demonstrated even in patients with normal pre-treatment uric acid
levels.[29-32] In two studies, the uric acid level was decreased to a normal range within four hours of
the patients' receiving rasburicase.[30,33] The rapid reduction in serum uric acid caused by rasburicase stands in contrast to the effect of
allopurinol (which merely decreases uric acid formation). Rasburicase promotes the degradation of
uric acid. Based on this fact, patients with pre-existing uric acid levels of ≥ 7.5 mg/dL should be
considered for its use. Rasburicase is an appropriate agent for the prevention of TLS. Overall, studies confirm that it is a
relatively safe drug with minimal incidence of side effects. However, one aspect of this agent that
precludes its use in many institutions, is its high cost.

Urinary alkalinization

Alkalinization promotes the conversion of uric acid to a more soluble urate salt, which in turn
decreases the potential for urate crystal precipitation. This is achieved only if the urine pH is
maintained ≥ 7. Agents such as sodium bicarbonate (50 to 100 mEq per liter of IV fluid) with
intravenous fluids or acetazolamide (200 to 500 IV daily) to stimulate an alkaline diuresis have been
used for this purpose. However, some studies suggest that hydration with intravenous fluids alone
may be just as effective at minimizing uric acid precipitation.[28] One potential downfall of urinary
alkalinization is that it may actually promote calcium phosphate deposition in renal tubules in
patients with hyperphosphatemia.[22,31] For this reason, alkalinization should be stopped if the
urine pH exceeds 7.5 or if serum uric acid levels have normalized. And a TLS expert panel
recommends alkalinization of the urine only in patients with metabolic acidosis.[34]

Dialysis

The role of dialysis in the prevention of tumor lysis syndrome in adults is unclear. However, two
studies have shown beneficial prophylactic effects in the pediatric population.[35,36]

Overview of Management

TLS, when clinically evident, is an emergency that can obviate the possibility of using chemotherapy
and can even result in death. Once TLS has developed, parameters such as heart rate, blood
pressure, urine output, respiration rate, serum uric acid level, serum electrolyte levels, and renal
function should be monitored every 6 hours for the first 24 hours. Other parameters—such as blood
cell count, serum lactate dehydrogenase level, serum osmolality, blood gases, acid-base equilibrium,
cardiac function (via electrocardiogram), and body weight—should be assessed every 24 hours. This
monitoring can be achieved most efficiently in an ICU or on a medical oncology floor with
well-trained staff.[13] If prophylaxis has failed, then therapy centers on correction of the metabolic disturbances.[3]
Patients must be aggressively hydrated with IV fluids. The target diuresis is at least 100 to 200
mL/hour (similar to the prophylaxis rate). Loop diuretics or mannitol may be used in conjunction with
aggressive fluid-loading to promote aggressive diuresis. Furosemide can be used for this purpose in
dosages of 20 to 100 mg IV every 4 to 8 hours or as an intravenous infusion of 10 to 20 mg/hour.[20]
Allopurinol, urate oxidase, and possibly urinary alkalinization all have a role in management.
Ultimately, dialysis may also be needed, especially if a patient exhibits severe or refractory acute
renal failure and/or symptoms from the metabolic derangements.
Management of Specific Metabolic Abnormalities

Hyperkalemia

Hyperkalemia must be treated rapidly and aggressively because of its potential for causing lethal cardiac arrhythmias. Administration of 50% dextrose in water and 10 units of regular insulin IV is the usual immediate treatment. This shifts potassium into the intracellular space. Oral binding resins (sodium polystyrene sulfonate) in a dose of 20 to 30 g every 6 to 8 hours can be administered in relatively mild cases (potassium level < 6 mEq/L). Loop diuretics can also be used to promote potassium excretion. If the hyperkalemia is refractory to these therapies or the potassium level is > 6 mEq/L (at which point cardiotoxicity becomes possible), hemodialysis is indicated.

Hyperphosphatemia/hypocalcemia

Initially, 20% dextrose in water with insulin should be given until the serum phosphorus level falls below 7 mg/dL. Phosphate binders can also be given to decrease the gut absorption of phosphate, but these agents may be of minimal benefit acutely. Aluminum hydroxide is one such agent and can be given orally (30 to 60 mL every 4 to 6 hours); this will bind any free phosphate in the intestine and prevent its absorption. Hemodialysis may be needed if the level exceeds 10 mEq/L. Correcting hypocalcemia via replacement is discouraged because of the risk of metastatic precipitation of calcium deposits (the calcium-phosphate product will already be increased). The administration of calcium gluconate for hypocalcemia is reserved for patients who exhibit symptoms of neuromuscular irritability such as tetany and/or seizures.[22]

Hyperuricemia/hyperuricosuria

In the event that prevention fails, therapy is similar to prevention methods. Treatment consists of the use of allopurinol, urate oxidase, and/or alkalinization of the urine. This abnormality is one potential cause of acute renal failure associated with TLS. Once renal failure develops, renal function usually is not restored until uric acid levels are brought down to less than 10 mg/dL. Role of urinary alkalinization. Urinary alkalinization is often used as a prophylactic measure. However, it is not a universal recommendation for the management of established TLS.[20,23] Allopurinol. Allopurinol is a key agent in the management of TLS. Allopurinol acts by competitively inhibiting xanthine oxidase, thereby preventing the conversion of xanthine to uric acid. When used for treatment, allopurinol is used in dosages similar to prophylactic dosages. If oral intake is not possible, 200 to 400 mg/m2/day intravenously can be used. One potential downside of this therapy is that in rare cases, treatment with allopurinol can still result in acute renal failure. Because allopurinol, via its metabolite oxipurinol, prevents the metabolism of xanthine to uric acid, xanthine accumulates. Build-up of xanthine has been shown to be a rare cause of renal failure. This complication may be avoided with good hydration. Another downside of this therapy is that allopurinol does not degrade the uric acid already present; thus, lower levels are not realized for at least 1 to 2 days.

Urate oxidase (rasburicase). This agent is not only used for the prophylaxis of TLS, but is also indicated for its treatment. The superior efficacy of rasburicase in the treatment of hyperuricemia associated with TLS has been demonstrated in many reports.[29,30,37] Studies comparing rasburicase to allopurinol for the treatment of TSL have shown better results with rasburicase. In fact, hyperuricemia can be reversed by the use of rasburicase after allopurinol failure.[38] Currently, the recommended dose of rasburicase is 0.15 to 0.2 mg/kg in 50 mL of isotonic saline infused over 30 minutes once daily; the average duration of therapy is two days but can vary from one to seven days. If the tumor lysis is massive, an increase of the dosage to twice daily may be needed. Recent data suggest that a single dose of 1.5 to 6 mg is effective at lowering the serum uric acid level in patients who are at risk for or who already have TLS.[39,40] It is very important to measure the serum uric acid level accurately in patients treated with rasburicase (the sample should be placed on ice while awaiting the assay); this is particularly true when a single low dose is used to modify the dosing and the duration of therapy. Patients being considered for rasburicase who potentially have glucose-6-phosphate dehydrogenase deficiency (G6PD), as indicated by the medical history, should be screened for G6PD; hydrogen peroxide, a product of uric acid breakdown, can cause severe hemolysis in patients with G6PD deficiency.

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Dialysis

Dialysis should be initiated early in patients with worsening renal failure despite optimal medical therapy. Congestive heart failure, potassium level > 6 mEq/L, serum creatinine level > 10 mEq/L, serum phosphorus level > 10 mEq/L, and/or serum uric acid level > 10 mEq/L are all indications for dialysis. Dialysis should also be considered in those patients who cannot establish sufficient diuresis on their own after a trial of aggressive fluid-loading and the use of loop diuretics.

In general, standard, intermittent hemodialysis is preferred to peritoneal dialysis because of its better efficacy in removing uric acid and phosphorus.[31] In the presence of hyperuricemia, dialysis may be useful for effectively bringing the uric acid levels down to < 10 to 20 mg/dL. With hemodialysis, uric acid clearance is 70 to 100 mL/min, and the plasma uric acid level can be decreased by approximately 50% with each six-hour treatment.[25] At this rate, renal function should start to recover. When used for severe hyperphosphatemia, hemodialysis can effect a phosphorus clearance rate of 60 to 100 mL/min, depending on the dialyzer and blood flow.

Intermittent hemodialysis has the drawback of poor control of serum phosphorus and rebound hyperkalemia.[41] Thus, other methods of dialysis have been under study. Continuous arteriovenous hemodialysis (CAVHD), continuous arteriovenous hemofiltration (CAVH), and continuous venovenous hemofiltration (CVVH) have demonstrated effectiveness in those patients who cannot tolerate conventional intermittent hemodialysis.[23,41,42] In patients with acute renal failure and mean arterial pressure of 60 mm Hg, the response seen with CAVHD has been shown to be at least equal
to that achieved with intermittent hemodialysis.[42] In another study, CAVHD at a high dialysate flow rate (4 L/hour) was actually found to be more efficacious than conventional intermittent hemodialysis.[41]

**Conclusion**

TLS is a major cause of morbidity and mortality in cancer patients worldwide and can be an economic burden to healthcare centers. Risk factor identification and prevention are the ideal modalities with which to approach this condition. Prevention of TLS will reduce mortality in already fragile patients. In cases where prevention fails, prompt and aggressive treatment of the various metabolic derangements associated with this syndrome is essential. Acute renal failure, seizures, and cardiac arrhythmias are the most lethal consequences of TLS. Effective prophylaxis and prompt, appropriate treatment should TLS develop can reduce healthcare costs by decreasing the number of intensive care days and by delaying dialysis.

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