Chapter 8
Tumor Lysis Syndrome

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List of Abbreviations

TLS	Tumor lysis syndrome
AKI	Acute kidney injury
ALL	Acute lymphoblastic leukemia
CML	Chronic myelogenous leukemia
NHL	Non-Hodgkin's lymphoma
CLL	Chronic lymphocytic leukemia

> Autopsy showed the usual findings of chronic myeloid leukemia. The kidneys were of particular interest. Both contained multiple uric acid and urate calculi in the calyxes, and the upper portion of the ureter was packed with gravel. -Merrill and Jackson, 1943 [1].

In health, cell death is a coordinated, orderly apoptotic process with resulting products readily managed by the usual homeostatic mechanisms. In contrast, when the rate of cell death is massive and there is cell lysis rather than apoptosis, the sudden release of large quantities of intracellular elements can overwhelm the homeostatic mechanisms and can cause dramatic shifts in body chemistry. This can occur during the treatment of high-grade, large-volume tumors, but can also spontaneously in the case of tumors with high intrinsic growth rates as the malignant cells proliferate, overgrow, and necrose [2]. The constellation of chemical and clinical abnormalities caused by the release of intracellular content from dying tumor cells is referred to as the tumor lysis syndrome (TLS). The major intracellular elements are potassium (leading to hyperkalemia), phosphate (leading to hyperphosphatemia and hypocalcemia), and nucleic acids, which are metabolized to uric acid and other products. These products of nucleic acid metabolism can form crystals in the urine and cause

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obstruction of urinary flow, one of the leading causes of acute kidney injury (AKI). As this obstruction may occur as radiolucent urate sludge in the tubules, it may not be apparent on radiologic images. Tumor cell death is also associated with the release of cytokines that may be of clinical import [3], but these are not typically considered part of the syndrome and will not be discussed further here.

History and Evolving Understanding

The first mention of treatment-related TLS was made nearly a century ago in a report of obstruction from uric acid crystals after radiotherapy of leukemia [4]. The risk of hyperuricemia, including kidney failure from urinary obstruction, quickly became more generally appreciated [5]. As treatments became more effective and measurements more precise, other metabolic complications were reported, including hyperkalemia and hyperphosphatemia (with associated hypocalcemia) soon after chemotherapy for Burkitt lymphoma [6, 7]. The observation that TLS can arise spontaneously in the absence of chemotherapy due to high cell turnover was later made in lymphoma [2]. That this syndrome was originally recognized in high-grade hematologic malignancies is presumably related to the high tumor burden and the rapid response to treatment in these diseases. However, in the last decades it has become apparent that TLS can appear in solid tumors as well, or after treatments other than standard chemotherapy.

Definition and Framework

Since the rate of cell death can be on a continuum from trivial to catastrophic, the exact point at which abnormalities reach the point of "TLS" is somewhat arbitrary. In addition, the clinical impact is affected by the body's fluctuating ability to manage the influx of intracellular products, since hemodynamic factors and kidney function can change during the course of illness. Nevertheless, in principle, TLS can be divided into three broad categories:

1. *No syndrome*, indicating that cell lysis occurs with only minor changes in body chemistries;
2. *Laboratory TLS*, where laboratory values are substantially abnormal but have not yet induced clinical manifestations; or
3. *Clinical TLS*, where disturbances reach a level that has clinical consequence or requires urgent intervention. This is generally a subset of the laboratory TLS category.

Several systems to formally define these categories have been proposed, [8] but the current classification for research and clinical purposes was established by Cairo and Bishop in 2004, [9] with minor modifications by later authors. In this classification system, laboratory values are assessed on days -3 to $+7$ relative to treatment

(Table 8.1). This system scores the severity of clinical symptoms and signs, for a grade of 0–5. Later, authors have suggested minor changes including the inclusion of symptomatic hypocalcemia as an additional criterion for clinical TLS [3], and the elimination of stages 0 (no disease) and 5 (death) [10].

Clinical Presentation

TLS is most commonly seen after directed therapy has caused rapid tumor cell death, but can also occur spontaneously. High-grade, aggressive tumors like Burkitt lymphoma or T-cell acute lymphoblastic leukemia (ALL) represent the majority of cases, but TLS may complicate other tumor types associated with large tumor burdens, rapid proliferation rates, or high sensitivity to chemotherapy. The first signs and symptoms may appear within 24–72 h of initiation of chemotherapy or embolization, but a more indolent course has been observed over weeks to months with spontaneous development of TLS.

Case #1
A 42-year-old man presented with 3 months of lethargy, malaise, intermittent low-grade fevers, and a 10-kg weight loss. He was actively treated with hydrochlorothiazide for hypertension diagnosed 4 years earlier. One week prior to presentation, he noted painful swelling in his neck, axillae, and groin, and 2 days earlier developed palpitations, restless legs, and paresthesias in his fingertips. On examination, his temperature was 38.7 °, heart rate 92 bpm, and blood pressure 96/62 mmHg. His conjunctivae were pale and mucous membranes dry. He had tender lymphadenopathy in both axillae, in the groin, and on neck exam in the posterior cervical chain. His heart rate was regular with frequent premature ventricular contractions. His lungs were clear. On abdominal examination, his liver span was slightly increased and tender, and a spleen tip was palpable at the level of the umbilicus. Extremities revealed 2+ dependent edema, scattered petechiae, and 2+ distal pulses. Cranial nerves were intact, but a Chvostek sign was noted upon tapping the left facial nerve. Laboratory testing identified potassium 6.6 mEq/L, bicarbonate 16 mEq/L, anion gap 22, creatinine 5.8 mg/dL, albumin 3.1 mg/dL, calcium 5.9 mg/dL, phosphate 18.7 mg/dL, and uric acid 21.3 mg/dL. Blood counts showed a white blood count (WBC) of 125 K with abundant blasts, hemoglobin 7.2 mg/dL, and platelets 17 K. Urinalysis demonstrated a specific gravity of 1.012, pH 5.5, 1+ protein and 2+ blood, and sediment with degenerating tubular cells and amorphous phosphate crystals. Because of progressive kidney failure, hyperkalemia, and dropping urine output in the setting of TLS, urgent dialysis was initiated. Computed tomography of the chest, abdomen, and pelvis identified

diffuse lymphadenopathy, and bone marrow biopsy confirmed the diagnosis of T-cell ALL.

Which of the following tumor types is least commonly associated with TLS?

a. Burkitt's lymphoma
b. T cell ALL
c. Non-Hodgkin lymphoma (NHL)
d. Breast cancer with high tumor load
e. Chronic myelogenous leukemia (CML)

Epidemiology and Risk Factors

As mentioned earlier, the majority of the reported cases have been observed in hematologic malignancies [11], although the incidence varies widely by tumor type. A series of 102 patients with NHL showed an overall incidence of nearly 50 % by laboratory values, although only 6 % met clinical criteria [8]. In an observational study of patients with acute myeloid leukemia (AML), 17 % had TLS (12 % by laboratory values alone and 5 % by clinical criteria as well) [12]. An incidence of 46 % has been reported in chronic lymphocytic leukemia (CLL) [13].

It has also become apparent that tumor lysis can occur in many situations other than hematologic malignancies being treated with standard chemotherapy. Tumor lysis has been reported in the treatment of solid cancers such as breast [14], melanoma [15], gallbladder [16], lung [17], liver [18], gastric or gastrointestinal [19, 20], pancreatic [21], yolk sac [22], prostate [23], colorectal [24], testicular [25], medulloblastoma [26], and sarcoma [27]; although the incidence with these tumors remains unknown due to the limits of case reporting. In addition, it has become apparent that the trigger need not be standard cytotoxic therapy, with TLS reported after treatment with steroids, biological agents such as rituximab or interferon [14, 28–31], embolization [18, 32], surgery/anesthesia [33, 34], and even vaccination [35]. A tumor lysis-like condition has been reported during the use of granulocyte colony-stimulating factor in the correction of leucopenia [36]. Clearly, it is important to be cognizant of this syndrome outside of the more traditional framework of hematologic malignancy.

Case #1 Follow-up and Discussion

The patient presented above has TLS. As discussed, all hematologic malignancies have been associated with TLS. Most of the cases of solid tumor-associated lysis occur in the setting of high tumor burden, and have been isolated case reports. Indolent cancers like CML rarely cause TLS.

Table 8.1 Criteria for laboratory and clinical TLS, modified from Cairo and Bishop 2004. (Modified Cairo-Bishop criteria (2004) [9], with modifications as suggested by Howard 2011 [3], Tosi 2008 [10], or Cairo 2010 [38] indicated in italics)

Laboratory TLS: two or more of (within −3 to +7 days relative to treatment)	Clinical symptoms (any of)	Clinical I	Clinical II	Clinical III	Clinical IV
Uric acid > 8 mg/dL (476 μmol/L) in adults, > age- normal in children Potassium > 6 mmol/L	Creatinine [9] *or* estimated kidney function [10][a]	< 1.5 × ULN, 30–45 ml/min	1.5–3xULN, 10–30 ml/min	3–6xULN, 10–20 ml/min	> 6 x ULN, < 10 ml/min or kidney replacement therapy
Phosphorous > 4.5 mg/dL (1.5 mmol/L) (adults) or > 6.5 mg/dl (2.1 mmol/L) (children)	Cardiac	Arrhythmia, no intervention	Nonurgent medical treatment	Symptomatic; incompletely controlled medically, or needing device (e.g., defibrillator)	Life-threatening with shock, syncope, hypotension, or CHF
Calcium: < 7 mg/dL, 1.75 mmol/L (corrected for albumin), or ionized < 1.12 mmol/L; *omitted by most recent schema* [38]	Neuromuscular	*Any symptomatic hypocalcemia* [3]*; grade not specified*	Single brief generalized seizure, rare focal motor seizures, or seizures well-controlled medically	Seizure with altered consciousness; generalized seizures despite medication	Repetitive seizures despite medication (e.g., status epilepticus)
Any of the above with > 25 % increase from recent baseline (or decrease for calcium) [9, 10, 38]; *others specifically exclude this Criterion* [3]					

CHF congestive heart failure, *ULN* upper limit of normal

[a]By an estimating equation (for adults, CKD-EPI, MDRD, or Cockcroft–Gault; for children, Schwarz)

Patient Risk Factors

Certain patient characteristics have been associated with an increased likelihood of developing TLS. Intuitively, the risk would be expected to be highest when tumor burden is large and in those diseases highly responsive to treatment. In a series of 328 children with ALL, TLS was noted in 74 (23 %). Factors predictive of TLS on a multiple regression analysis included age ≥ 10 years (OR 4.5), the presence of splenomegaly (OR 3.3) or a mediastinal mass (OR 12.2), and WBC $\geq 20 \times 10^9$/L (OR 4.7) [37]. Other authors studying AML have reported an association with high LDH, WBC count over 25×10^9/L, as well as an elevated creatinine and uric acid [12]. The usefulness of these predictors has generally not been studied in validation cohorts or in patients with malignancies other than those from which the predictors were derived. Nevertheless, there have been several risk stratification algorithms proposed [38−40] which involve the general consideration of laboratory values, tumor type, and preexisting chronic kidney disease.

As previously mentioned, the presentation of TLS may occur with either abnormal laboratory parameters or the clinical manifestations of these disturbances. The *laboratory presentation* results from the release of intracellular molecules into the plasma, or the secondary effect of these chemicals on serum calcium levels. The abnormalities of the laboratory presentation according to the Cairo–Bishop criteria are listed in Table 8.1, and include the presence of two or more of hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia. Nucleic acids, potassium, and phosphates are in high concentration in the intracellular environment, and released into the plasma under circumstances of rapid and extensive cell death. Hypocalcemia is a secondary effect of released phosphates complexing with plasma calcium and depositing in soft tissues and interstitial spaces. This typically occurs when the calcium-phosphate product reaches levels greater than $60\,mg^2/dl^2$.

The *clinical presentation* occurs when symptoms and signs develop as a result of these changes. Generalized symptoms of anorexia, nausea, vomiting, diarrhea, and lethargy are common. Cardiac complications, including cardiac dysrhythmias, heart failure, syncope, and possible sudden death, may reflect hyperkalemia, hypocalcemia, and deposition of calcium-phosphate in the myocardium, disrupting contractility and electrical conduction. Neuromuscular effects include muscle spasms, tetany, and seizures.

The manifestations of TLS in the kidney include AKI, hematuria, oliguria, flank pain, and nephrolithiasis. The development of AKI is related to a variety of factors, including renal vasoconstriction, disrupted autoregulation, reduced renal blood flow, inflammation, tubular epithelial cell injury, and intra tubular deposition and obstruction by crystals. Uric acid and calcium-phosphate deposition within the renal pelvis or as ureteral stones may be responsible for many of these clinical manifestations. The urinalysis often demonstrates uric acid crystals or amorphous urate in acidic urine. The kidney pathology includes calcium-phosphate crystals in the interstitium (Fig. 8.1a) and uric acid crystals resulting in tubular obstruction (Fig. 8.1b). Xanthine is another poorly soluble metabolite of purine metabolism that can deposit in tissues.

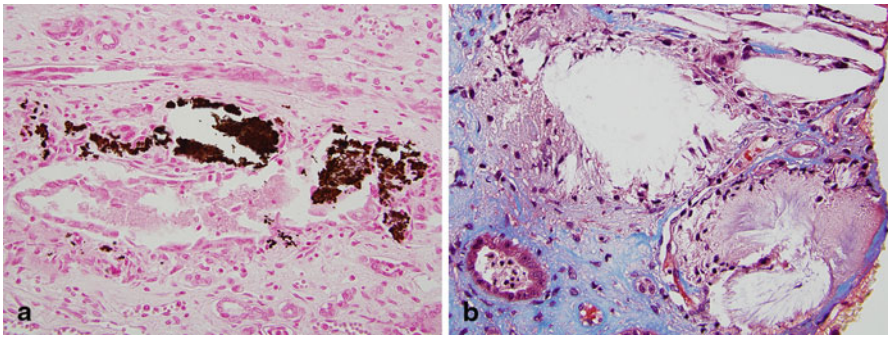

Fig. 8.1 Panel **a** shows cortical tubules with injury and calcium-phosphate deposition in the lumen, epithelium, and interstitium. Von Kossa stain demonstrates-phosphate (but not oxalate) deposition (original magnification 40 ×). Panel **b** shows urate deposits in renal medulla (Masson Trichrome, original magnification 40 ×)

Outcomes

The development of TLS is associated with a series of clinical complications, including prolonged hospitalization, increased morbidity, and reduced survival. In a retrospective series of 772 patients with AML, clinical TLS (but not laboratory TLS) was associated with a 79 % risk of death (30 of 38 patients) versus 23 % in those who failed to meet criteria. This mortality included kidney failure, arrhythmias, and coma felt to be directly attributable to TLS [12].

Though not specifically addressing tumor lysis as a cause, the development of AKI complicating treatment of hematologic malignancies (excluding Hodgkin's disease) has been identified as a major factor in prolonged hospitalization and higher inpatient medical costs. Analysis of data on over 400,000 patients from the Health Care Utilization Project revealed patients who developed AKI requiring dialysis, developed AKI without dialysis, and had no kidney complications has mean hospital stays of 17.6, 12.2, and 7.4 days, with hospitalization costs (in 2006 dollars) of $ 44,619, 25,638, and 13,947, respectively [41].

In another European analysis of 755 patients with ALL, AML, or NHL, 27.8 % met criteria of TLS. Patients requiring dialysis for TLS had hospitalization costs 26-fold greater than patients who developed hyperuricemia without fulfilling criteria for TLS or requiring dialysis. Death was attributable to TLS in 15 (2 %) patients [42].

Pathophysiology and Pathology

As noted, the laboratory and clinical manifestations of TLS result from the release of intracellular contents such as nucleic acids, potassium, phosphates, and other chemicals after extensive tumor lysis which results in a cascade of pathologic and

pathophysiologic processes. The intracellular concentration of potassium is approximately 150 mEq/L, and cellular damage results in the spillage of this potassium into the extracellular space and plasma. This hyperkalemia may disrupt the Nernst potential governing cellular depolarization, opening voltage-gated sodium channels before inactivating the same channels. This action impairs neuromuscular, cardiac, and gastrointestinal function, thereby affecting cardiac conduction and inciting ventricular arrhythmias and asystole.

Phosphate is the most abundant intracellular anion, found primarily as adenosine phosphates (AMP, ADP, and ATP) and in DNA and RNA. Furthermore, tumor cells may have a phosphate content greater than four times that of normal cells [43]. The clinical manifestations of an extracellular phosphate load induced by extensive cell death are typically kept in check by the high capacity of the kidney to excrete phosphate. However, in the setting of reduced kidney function or simultaneous kidney injury as occurs in TLS, phosphate accumulation results in hyperphosphatemia. The direct clinical manifestations of hyperphosphatemia are limited, but extracellular phosphate complexes with ionized plasma calcium and deposits as calcium-phosphate crystals in the kidneys, vasculature, and soft tissues. This results in a fall in plasma concentrations of free calcium and clinical hypocalcemia. Since calcium inhibits sodium channels and depolarization of nerves and muscles, acute hypocalcemia lowers the threshold for depolarization and clinically manifests as tetany, seizures, hyperreflexia, cardiac arrhythmias, and possibly death. Tetany is neuromuscular irritability and hyperexcitability, with symptoms ranging from perioral numbness and paresthesias to carpopedal spasm and laryngospasm. Trousseau sign (carpopedal spasm induced by inflation of a sphygmomanometer above systolic blood pressure for 3 min) and Chvostek sign (contraction of the ipsilateral facial muscles elicited by tapping the facial nerve just anterior to the ear) are two of the more common features of tetany in hypocalcemia. The cardiac complications of hypocalcemia include impaired inotropy leading to reversible heart failure, and electrophysiologic derangements from prolonged QT interval to heart block and ventricular arrhythmias. Other manifestations of hypocalcemia in TLS include psychiatric lability, mood instability, and papilledema.

The effects of calcium and phosphate deposition in the kidney induce a variety of insults. Calcium-phosphate crystals that deposit in tubular lumina can result in urinary obstruction. In addition, these crystals appear within tubular epithelial cells where they exert direct tubular toxicity and in the interstitium where they incite an inflammatory response. This is evident on kidney biopsy that demonstrates localization of phosphate using von Kossa stain in the lumen of the distal tubule, with lesser deposits in the tubular interstitium and in the epithelial cells (Fig. 8.1a). Tubular atrophy, tubular necrosis, and nephrocalcinosis are consequences of calcium-phosphate deposition. In the current era of uric acid-lowering therapy, calcium-phosphate deposition presumably represents an increasingly important contributor to kidney damage.

Nucleic acids are also released following cellular destruction. Purines undergo a series of reactions resulting in their degradation, with guanosine metabolized by purine nucleoside phosphorylase to guanine, and then by guanine deaminase into xanthine (Fig. 8.2). Adenosine is metabolized by adenosine deaminase into inosine,

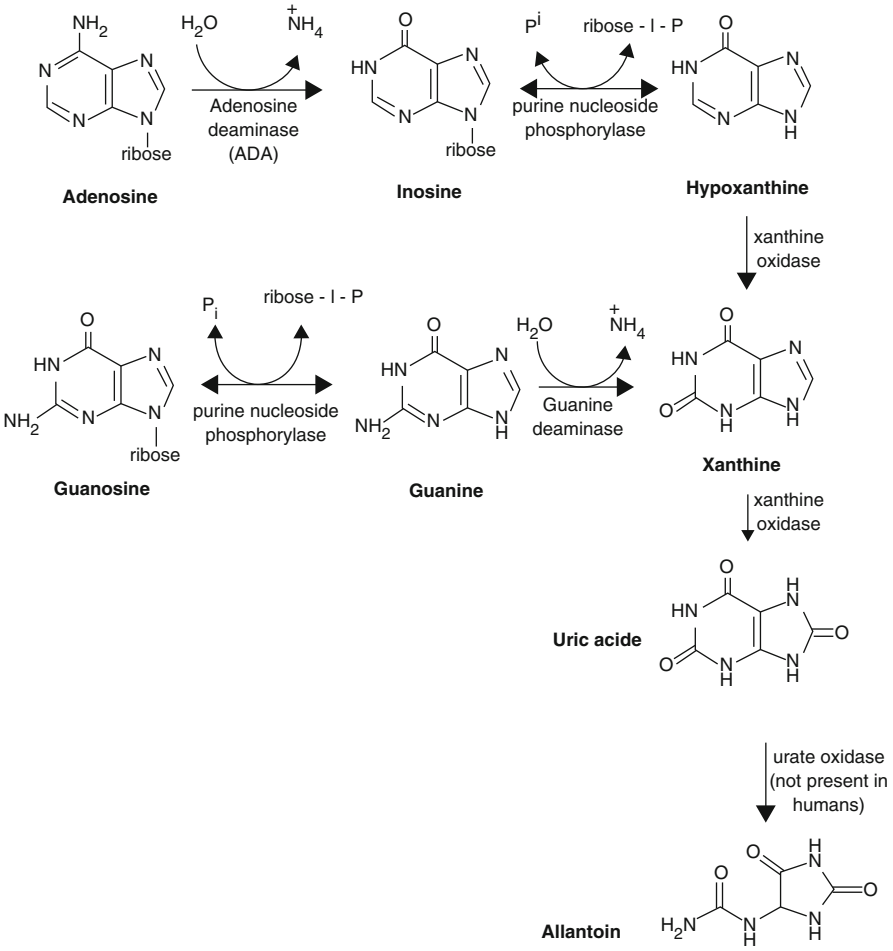

Fig. 8.2 Purine metabolism

and then purine nucleoside phosphorylase into hypoxanthine. Hypoxanthine is first converted to xanthine by xanthine oxidase, before xanthine is metabolized into uric acid. Uric acid is a weak acid with a pK_a of 5.75. This means that at a physiologic pH of 7.4, 98 % of uric acid is in its ionized form of urate. In the acidic environment of the distal tubule where the pH falls below 5.0, equilibrium favors the less-soluble protonated form of uric acid that precipitates as crystals. The large load of filtered urate in TLS along with its rising concentration along the length of the tubule results in tubular precipitation in the increasingly acidic environment of the distal tubule. This leads to obstruction of tubules, collecting ducts, and even pelvises and ureters.

The precipitation of uric acid in the tubules is enhanced by the presence of a calcium-phosphate crystal nidus, and conversely, calcium-phosphate precipitation

is enhanced by the presence of uric acid crystals. Together, high concentrations of calcium-phosphate and uric acid potentiate the risk of AKI.

Tubular obstruction from crystal deposition induces a cascade of processes that result in AKI. Increased tubular pressure raises intrarenal pressure and compresses venous channels within the kidney. The increase in vascular resistance reduces renal blood flow. Together, high tubular pressures and reduced renal blood flow lower glomerular filtration rate.

Case #2

A 14-year-old girl presented to her pediatrician with 1 week of abdominal bloating, nausea, vomiting, and malaise. She had previously been well, but the distension occurred rapidly and resulted in extreme discomfort. On examination, her temperature was 38.2 C, heart rate 110 bpm, and blood pressure 86/68 mmHg. Her oropharynx was clear and no cervical lymphadenopathy was present. Her heart was regular, and her lungs were clear. Her abdomen was distended and diffusely tender, with a palpable fluid wave. An epigastric mass was appreciated. Axillary and femoral lymphadenopathy was absent. Extremities revealed 2+ dependent edema. Laboratory testing showed potassium of 3.1 mEq/L, bicarbonate 22 mEq/L, creatinine 0.8 mg/dL, eGFR 111 ml/min/1.73 m^2 by the CKD-EPI equation, albumin 4.2 mg/dL, calcium 8.6 mg/dL, phosphate 1.2 mg/dL, and LDH 850 U/L. Blood counts showed a WBC of 125 K, hemoglobin 13.8 mg/dL, and platelets 229 K. Computed tomography of the abdomen demonstrated ascites and a 14-cm mass compressing the antrum of the stomach. Biopsy of the abdominal mass showed monomorphic, medium-sized cells with round nuclei, multiple nucleoli, and basophilic cytoplasm. Cell surface expression of CD19, CD20, CD22, CD79a, CD10, HLA-DR, and CD43 confirmed the diagnosis of Burkitt lymphoma. Treatment with EPOCH with rituximab was considered, but prophylaxis for TLS was first felt necessary.

What agent would you recommend for prevention of TLS?

a. Volume expansion with bicarbonate based fluids
b. N-acetyl-L-cysteine
c. Recombinant urate oxidase
d. Allopurinol

Prevention and Treatment

Although guidelines for the management of TLS exist, they are not grounded on large quantities of clinical trial data given the relatively rarity of the condition [39]. In general, the therapies for TLS are more effective when used for prevention, in

part because kidney failure may not be readily reversed. Therefore, the mainstay is recognizing the possibility of tumor lysis and implementing an early and liberal administration of inexpensive preventative measures. There are additional therapies, either given preventatively to patients at particular risk or therapeutically as warranted by developments in the clinical course.

There are three major therapies available for prevention or treatment of TLS: volume expansion (with or without forced diuresis), allopurinol, and recombinant urate oxidase.

Volume Expansion

Hypovolemia and reduced kidney function are risk factors for developing TLS, and the early and copious administration of intravenous fluid is a mainstay of TLS treatment. The goal is not so much volume expansion per se, but the optimization of kidney function and the initiation of a brisk diuresis. A high urinary flow rate causes the daily burden of uric acid, phosphate, and other metabolites to be less concentrated in the urine and therefore less likely to precipitate into obstructing crystals. In addition, uric acid handling by the proximal tubule is coupled to sodium transport, such that volume contraction and the accompanying sodium avidity increase urate reabsorption and diminish its urinary clearance. Conversely, circumstances of adequate volume expansion and reduced tubular sodium reabsorption are associated with reduced urate reabsorption and enhanced excretion.

In general, aggressive intravenous fluid resuscitation is indicated for nearly everyone in whom tumor lysis is considered. By clinical practice, the administered fluid tends to be dextrose/quarter-normal saline in children [44], and isotonic or dextrose/half-normal saline in adults, but can be tailored to the individual patient. Assuming that there is no contraindication such as heart failure, the rate of fluid administration can be quite high: 2–3 L/day/m^2 BSA [40] starting 2 days before and lasting until 3 days after chemotherapy [45].

Though it has not been studied in a controlled manner, diuretics have been used on a theoretical basis to maintain urinary flow at a rate of 100 ml/m^2 BSA/h [3, 9]. It is important to appreciate that the goal is high urine flow, not actual negative fluid balance. Diuretics should only be considered in adequately volume loaded patients who are simultaneously receiving intravenous fluids.

Because of the increased solubility of uric acid in alkaline urine, prior practice was to routinely administer sodium bicarbonate with the goal of raising urine pH, increasing urate solubility, and reducing uric acid precipitation. However, concerns were later raised that this may *reduce* solubility of calcium-phosphate complexes, which can also be a cause of kidney failure with tumor lysis [46]. In addition, hypocalcemia is common in tumor lysis, and alkalinization of the serum may reduce the ionized fraction of calcium and worsen the symptoms of hypocalcemia [47]. More recent guidelines, therefore, no longer recommend routine prophylactic alkalinization in the treatment of TLS [39]. Of course, this does not preclude the use of alkalinization

when specifically indicated for other clinical reasons, for example, in the urgent treatment of hyperkalemia or metabolic acidosis, the latter occurring in the setting of severe TLS in patients with evolving AKI .

Allopurinol

Allopurinol is an inhibitor of xanthine oxidase that reduces the conversion of xanthine to uric acid (see Fig. 8.2). When given intravenously as prophylaxis, it has prevented an increase in uric acid levels in most patients at risk for TLS [48]. The doses used in children and adults are weight-based up to a maximum of 600 mg IV or 800 mg orally per day, given in divided doses. Dose reduction is required in the presence of kidney disease. Therapy is started 1–2 days before chemotherapy and is continued until 3–7 days after its conclusion [39]. Though there is no specific advantage to the intravenous route of administration, it allows more reliable dose delivery than the oral form in patients with gastrointestinal issues related to disease or treatment.

There is extensive experience with allopurinol, and it is recommended for use in patients at intermediate risk of tumor lysis [40]. However, allopurinol has the disadvantage that it cannot affect uric acid that has already been generated. It may also lead to an increase in uric acid precursors such as xanthine, which themselves may precipitate in the kidney [49]. In addition, allopurinol has multiple drug interactions and may require dose adjustments or avoidance with certain chemotherapeutic agents or other medications.

Rasburicase

The rapid degradation of uric acid into highly soluble allantoin is possible enzymatically by urate oxidase (see Fig. 8.2), but this enzyme is absent in primates. The use of nonrecombinant urate oxidase (uricosyme) was an early approach to address this deficiency [50]. While effective in lowering uric acid levels, it had an incidence of severe allergic reactions in nearly 5 % of patients [51]. In 2001, a recombinant form of urate oxidase, rasburicase, was reported as highly effective in controlling uric acid levels when compared to allopurinol, with a low rate of adverse events [52]. It is extremely effective with nearly all patients reaching normal or low levels of uric acid [53, 54]. In addition, unlike allopurinol, it can eliminate pre-formed uric acid rather than simply prevent more formation. Rasburicase was initially FDA-approved in the USA in 2005 for the treatment and prevention of tumor lysis-related hyperuricemia in children [55], and in adults in 2009.

Since its initial introduction, there has been some evolution in its role. After additional reporting, it is still considered a safe therapy with relatively few adverse reactions. However, its action involves the production of hydrogen peroxide, and in patients with G6PD deficiency can be associated with the development of methemoglobinemia and hemolytic anemia; it is contraindicated in patients with

this condition [56, 57]. There are also reports of the development of anti-rasburicase antibodies, though the clinical significance of this is unclear with no hypersensitivity reactions during the initial course of therapy [53, 58]. Meta-analyses of the adult and pediatric literature have not shown definite improvement in kidney failure or death outcomes [54, 59], but given the dramatic metabolic improvements, rasburicase has established itself in guidelines and clinical practices.

The major limitation to the use of rasburicase is its cost. The label recommends a dose of 0.2 mg/kg for up to 5 days, with costs in the many thousands of dollars [42]. This makes it potentially prohibitive for routine use. In a European cost-effectiveness analysis of ALL/NHL/AML patients with an overall incidence of TLS around 5 %, rasburicase *treatment* of established tumor lysis was cost-saving in most cases [42]. In children, *preventive* use of rasburicase was highly cost effective with an estimated incremental cost of 445–3054 € per life-year saved. In adults, the incremental cost per life-years saved by preventive use was 41,383 € in NHL, 32,126 € in ALL, and close to 100,000 € in AML, due to the limited survival of these patients. Others have explored whether reduced dosing might be effective. For example, a dose of 0.15 mg/kg/day [53] or a 3 mg fixed dose [60−62] in children has been tested. Others have proposed a 3-day course instead of 5 days (with follow-up allopurinol), or single-dose protocols (repeated as necessary for uric acid > 7.5 mg/dL) for adults using 6 mg [63] or 0.15 mg/kg doses [55]. In a single-dose randomized trial, only 6 of 40 (15 %) patients in the single-dose arm required a second dose. Outcomes were similar to the daily dosing arm, but with fewer side effects. Patel has pointed out that a 1-day course of rasburicase might even be less expensive than a multiple-day course of intravenous allopurinol in patients unable to take oral medication, once the costs of administration are taken into account [64]. In summary, it appears that rasburicase is highly effective, but the minimum effective dose to achieve adequate results is still an area of exploration.

Case #2 Follow up and Discussion

The 14-year-old girl is at high risk of TLS. Volume expansion with normal saline to maintain a urine flow rate of 2–3 L/day would be beneficial in preventing the syndrome. Diuretics should only be considered in adequately volume expanded patients who are simultaneously receiving intravenous fluids. Bicarbonate-based fluids reduce the solubility of calcium-phosphate complexes, which can also be a cause of kidney failure with tumor lysis [46]. In addition, hypocalcemia is common in tumor lysis, and alkalinization of the serum may reduce the ionized fraction of calcium and worsen the symptoms of hypocalcemia [47]. More recent guidelines, therefore, no longer recommend routine prophylactic alkalinization in the treatment of TLS [39]. In children, preventive use of rasburicase was highly cost-effective with an estimated incremental cost of 445–3054 € per life-year saved. It is extremely effective with nearly all patients reaching normal or low levels of uric acid [53, 54], making this the best of the options given.

Medical Management of Electrolyte Abnormalities

In general, the management of hyperkalemia related to TLS is not different from the management of hyperkalemia from other causes. Hypocalcemia should be treated if symptomatic with intravenous calcium gluconate. However, if the patient is asymptomatic, supplementation should generally be avoided as hyperphosphatemia may lead the administered calcium to simply complex and precipitate without benefit (but some risk) to the patient. Hyperphosphatemia, if severe, can be treated with oral phosphate binders such as a short course of aluminum hydroxide, though there are no studies testing its specific role in TLS [3]. For the reason just described, calcium-based phosphate binders should generally be avoided.

Kidney Replacement Therapy

The use of prophylactic kidney replacement therapy has been explored in patients at particularly high risk, using continuous venovenous hemofiltration [65]. This prophylactic approach was associated with improved control of laboratory values, as expected. However, in general, kidney replacement is reserved for situations where it is clinically required for treatment rather than as prophylaxis. There is no specific evidence to favor continuous versus intermittent kidney replacement therapy, though it is worth noting that the continuous therapies tend to have a more effective clearance of phosphate if that is a particular clinical concern.

General Strategy

A strategy for identifying prophylaxis for patients at different risk for tumor lysis has been outlined in a consensus guideline by Cairo et al., among others [38]. Risk is stratified into low ($< 1\,\%$), intermediate (1–5 %), and high ($> 5\,\%$) on the basis of tumor type, lab values, and patient characteristics. The algorithm is complex, but overall recommends the use of monitoring and intravenous fluids in all patients, with low-risk patients considered for prophylactic allopurinol; intermediate-risk patients treated with prophylactic allopurinol; and high-risk patients treated with prophylactic rasburicase [38]. An example from the consensus guidelines for specific diseases is reproduced in Table 8.2, with more detail available in the full guidelines. A closely related schema has been proposed by Tosi et al. (2008) [10].

Table 8.2 Consensus guidelines for treatment and prevention of TLS. (Reproduced from Cairo 2010) [38]

Low-risk disease	Intermediate-risk disease	High-risk disease
ST[a]	N/A	N/A
MM	N/A	N/A
CML	N/A	N/A
Indolent NHL	N/A	N/A
HL	N/A	N/A
CLL[b]	N/A	N/A
AML and WBC $< 25 \times 10^9$/L and LDH $< 2 \times$ ULN	AML with WBC 25–100 $\times 10^9$/L AML with WBC 25 $\times 10^9$/L and LDH $\geq 2 \times$ ULN	AML and WBC $\geq 100 \times 10^9$/L
Adult intermediate grade NHL and LDH $< 2 \times$ ULN	Adult intermediate grade NHL and LDH $\geq 2 \times$ ULN	N/A
Adult ALCL	Childhood ALCL stage III/IV	N/A
N/A	Childhood intermediate grade NHL stage III/IV with LDH $< 2 \times$ ULN	N/A
N/A	ALL and WBC $< 100 \times 10^9$/L and LDH $< 2 \times$ ULN	ALL and WBC $\geq 100 \times 10^9$/L and/or LDH $\geq 2 \times$ ULN
N/A	BL and LDH $< 2 \times$ ULN	BL stage III/IV and/or LDH $\geq 2 \times$ ULN
N/A	LL stage I/II and LDH $< 2 \times$ ULN	LL stage III/IV and/or LDH $\geq 2 \times$ ULN
N/A	N/A	IRD with reduced GFR and/or kidney involvement IRD with uric acid, potassium and/or phosphate ULN
Prophylaxis recommendations		
Monitoring	Monitoring	Monitoring
Hydration	Hydration	Hydration
± Allopurinol	Allopurinol	Rasburicase[c]

ST solid tumors, *MM* multiple myeloma, *CML* chronic myeloid leukemia, *NHL* non-Hodgkin lymphoma, *HL* Hodgkin lymphoma, *CLL* chronic lymphoid leukemia, *AML* acute myeloid leukemia, *WBC* white blood cell count, *LDH* lactate dehydrogenase, *ULN* upper limit of normal, *ALCL* anaplastic large cell lymphoma, *N/A* not applicable, *ALL* acute lymphoblastic leukemia, *BL* Burkitt lymphoma/leukemia, *LL* lymphoblastic lymphoma, *IRD* intermediate risk disease

[a]Rare solid tumors, such as neuroblastoma, germ cell tumors, and small cell lung cancer or others with bulky or advanced stage disease, may be classified as IRD

[b]CLL treated with fludarabine, rituximab, and/or those with high WBC (‡50 · 109/l), should be classified as IRD

[c]Contraindicated in patients with a history consistent with glucose-6 phosphate dehydrogenase. In these patients, rasburicase should be substituted with allopurinol

Summary

TLS is a potentially serious complication during the treatment of tumors, particularly in patients with high grade cancer and large tumor burden. Practitioners need to be aware that it can arise during treatment of nearly any tumor, and though usually related to treatment, can arise spontaneously. Prophylactic measures include administration of intravenous fluids, with escalating therapies to lower uric acid guided by clinical risk. Though evidence is limited, there are multiple guidelines and scoring systems to assist practitioners in directing therapy.

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