Review Article

Prevention and Treatment of Tumor Lysis Syndrome in the Era of Onco-Nephrology Progress

Joanna Matuszkiewicz-Rowinska Jolanta Malyszko

Department of Nephrology, Dialysis and Internal Diseases, Medical University of Warsaw, Warsaw, Poland

Keywords

Tumor lysis syndrome · Acute kidney injury · Hyperuricemia · Hyperphosphatemia · Allopurinol · Rasburicase

Abstract

Background: Tumor lysis syndrome (TLS) is an oncologic emergency due to a rapid break down of malignant cells usually induced by cytotoxic therapy, with hyperuricemia, hyperkalemia, hyperphosphatemia, hypocalcemia, and serious clinical consequences such as acute renal injury, cardiac arrhythmia, hypotension, and death. Rapidly expanding knowledge of cancer immune evasion mechanisms and host-tumor interactions has significantly changed our therapeutic strategies in hemato-oncology what resulted in the expanding spectrum of neoplasms with a risk of TLS. **Summary:** Since clinical TLS is a life-threatening condition, identifying patients with risk factors for TLS development and implementation of adequate preventive measures remains the most critical component of its medical management. In general, these consist of vigilant laboratory and clinical monitoring, vigorous IV hydration, urate-lowering therapy, avoidance of exogenous potassium, use of phosphate binders, and – in high-risk cases – considering cytoreduction before the start of the aggressive agent or a gradual escalation of its dose. **Key Messages:** In patients with a high risk of TLS, cytotoxic chemotherapy should be given in the facility with ready access to dialysis and a treatment plan discussed with the nephrology team. In the case of hyperkalemia, severe hyperphosphatemia or acidosis, and fluid overload unresponsive to diuretic therapy, the early renal replacement therapy (RRT) should be considered. One must remember that in TLS, the threshold for RRT initiation may be lower than in other clinical situations since the process of cell breakdown is ongoing, and rapid increases in serum electrolytes cannot be predicted.

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Jolanta Malyszko
Department of Nephrology, Dialysis and Internal Medicine
Warsaw Medical University, Banacha 1a
PL-02-097 Warsaw (Poland)
jolmal@poczta.onet.pl

Fig. 1. Diagnosis of TLS in adults [2, 3]. TLS, tumor lysis syndrome; AKI, acute kidney injury; ULN, upper limit of normal.

Laboratory diagnosis of TLS <i>*at least 2 criteria observed within a 24-hour period</i>	Clinical diagnosis of TLS <i>*laboratory diagnosis + at least one clinical criterion needed</i>
<ol style="list-style-type: none"> 1. Uric acid >8 mg/dl (475 μmol/l) 2. Phosphate >4.5 mg/dl (1.5 mmol/l) 3. Potassium >6.0 mmol/l 4. Corrected calcium <7 mg/dl (1.75 mmol/l) or Ca^{++} <4.5 mg/dl (1.12 mmol/l) 	<ol style="list-style-type: none"> 1. Acute kidney injury defined as creatinine $\geq 1.5 \times$ upper limit of normal - or - its increase of ≥ 0.3 g/dl (26.5 μmol/l) - or - diuresis <0.5 ml/kg/hr for 6 hr 2. Cardiac dysrhythmia, sudden death probably or definitely caused by hyperkalemia 3. Cardiac dysrhythmia, sudden death, seizure, neuromuscular irritability (overt and latent tetany, muscle twitching, paresthesias, broncho- and laryngospasm), hypotension or heart failure probably/definitely caused by hypocalcemia

Introduction

Tumor lysis syndrome (TLS) is a hemato-oncologic emergency, characterized by hyperuricemia, hyperkalemia, hyperphosphatemia, hypocalcemia, and metabolic acidosis. It is due to a rapid break down of malignant cells, with a massive release of intracellular contents: potassium, phosphate, nucleic acids, and cytokines into the bloodstream. Catabolism of the nucleic acids leads to hyperuricemia, while hypocalcemia is a consequence of acute hyperphosphatemia with phosphate binding to calcium and calcium phosphate deposition in the body tissues. All this may be accompanied by a systemic inflammatory response triggered by cytokines released from tumor cells.

Usually, TLS is induced by cytotoxic therapy and appears in the first 48–72 h after its initiation, with first laboratory signs usually observed already 6–24 h after its initiation. However, it may be spontaneous, as in the case of rapidly proliferating high-grade hematologic malignancies, such as Burkitt's lymphoma, acute myeloid leukemia (AML), and anaplastic large T-cell or diffuse large B-cell lymphoma [1]. TLS may have only laboratory form, or the metabolic disturbances may overwhelm the patient's homeostatic capacity, leading to severe clinical consequences such as acute kidney injury (AKI), cardiac arrhythmia, hypotension, and/or neurologic complications, called then clinical TLS. The criteria for the diagnosis of both laboratory and clinical TLS are presented in Figure 1 [2, 3].

The Incidence of TLS

The incidence and prevalence of TLS are not well defined since they vary depending on several tumor-, anticancer therapy-, and patient-related risk factors, as well as prophylactic procedures undertaken. The most epidemiological data come mostly from the 90s, with laboratory TLS described in about 40% adults with hematologic malignancies [4] and even up to 70% of children with acute leukemia [5] and clinical form in <10% [6–8]. Then, in the first-year decade of the 21st century, we witnessed a rapid growth of highly effective novel anti-cancer therapies, and the risk of TLS – at least in certain diseases like chronic lymphocytic leukemia (CLL) – seemed to be even higher. This early experience resulted in the development of strict preventive measures and step-wise dosing and therapeutic sequencing strategies, which remarkably decreased the incidence of TLS [9]. It is now much less common, provided the adequate prophylaxis and monitoring; however, it must be kept in mind that the consequences may be fatal if they happen.

The Outcome of TLS

The condition is life threatening, and when not recognized early enough and aggressively treated, it is linked to a significantly increased risk for poor outcomes, with overall in-hospital mortality ranging in different series from 21 to 32%, with the highest reported rates of 79% in AML patients during induction therapy [6, 10, 11]. Among many predictors of short- and long-term mortality in patients with TLS, AKI appears to be the important one. In a single-center study in France, in-hospital and 6-month mortality rates were significantly higher in patients with TLS-related AKI (51 and 66%, respectively) than in patients with TLS but without AKI (7 and 21%) [11]. After adjustment for acute disease severity, the presence of AKI was associated with higher hospital mortality (OR: 10.41; 95% CI: 2.01–19.170; $p = 0.005$) and 6-month mortality (OR: 5.61; 95% CI: 1.64–54.66; $p = 0.006$), compared to patients without renal injury.

Long-term outcomes of TLS and TLS-related AKI are much more challenging to evaluate since there are too many confounding factors, with underlying malignancy being one of the most important. TLS-induced AKI may also decrease the probability of getting a long-term remission of the malignancy. No studies to date have evaluated the renal recovery from this specific type of AKI. It is known that AKI is a strong, independent risk factor for later CKD development and long-term mortality [12, 13]. Therefore, the role of early and adequate prophylaxis is crucial. Although there are no hard data, the studies performed in the last decade strongly suggest that the incorporation of strict preventive measures such as vigorous hydration, urate-lowering therapy, and close monitoring of the patient, together with more sophisticated cancer treatment strategies, may significantly reduce the risk, hasten recovery, and prevent complications.

AKI in TLS

The AKI is usually oliguric, and it is mostly a crystal-dependent injury due to precipitation of uric acid and calcium phosphate in renal tubules with obstruction of the tubular lumen. Calcium phosphate also precipitates in the interstitium and renal microvasculature, leading to nephrocalcinosis. Both types of crystals are toxic to the tubular epithelium, inducing local active inflammatory and pro-oxidative responses [14, 15]. Soluble uric acid may induce hemodynamic changes, with decreased renal blood flow due to vasoconstriction and impaired autoregulation (crystal-independent pathway) [15].

Additionally, uric acid may interfere with regenerative processes in proximal tubule cells, affecting their proliferation [16]. The aggravating factors include volume depletion, hypotension, nephrotoxins, radio-contrast exposure, sepsis, and pre-existing kidney dysfunction. In patients treated with high doses of allopurinol, the urinary concentration of xanthine may exceed its solubility leading to xanthine nephropathy or urolithiasis [17].

How to Effectively Prevent TLS and AKI

Since TLS is a life-threatening complication, prevention is the key component of its medical management. A simplified 3-step algorithm for the prevention of TLS is presented in Figure 2. The first step is to identify patients with risk factors for TLS development, the second is to implement adequate prophylactic measures that reduce the risk, and the third is a vigilant laboratory and clinical monitoring.

Fig. 2. Key steps in TLS prevention. TLS, tumor lysis syndrome; CKD, chronic kidney disease; LDH, lactate dehydrogenase; RRT, renal replacement therapy.

Risk Stratification

Every patient who is going to receive chemotherapy for any hemato-oncological malignancy should be assessed for the risk of TLS. The risk depends on (1) the type of cancer, its mass, and cell-lysis potential; (2) the anticancer regimen, its effectiveness, and dosing; and (3) the clinical condition of the patient, particularly the presence of kidney dysfunction or involvement by the disease (Fig. 3).

Cancer-Related Factors

In general, due to a rapid rate of cell turnover and sensitivity to chemotherapy, TLS has been observed more often in patients' hematologic malignancies [18]. The highest risk of TLS has been described in patients with Burkitt lymphoma, other rapidly growing high-grade non-Hodgkin lymphomas, B-cell acute lymphoblastic leukemia, AML with high white blood counts ($>50K$), and – more recently – in CLL and when treated with newer anticancer therapies. In patients with high-grade non-Hodgkin lymphomas, the predisposing cancer-related factors that must be assessed include the disease bulk, advanced stage, cancer and its proliferation potential (indicated by serum LDH $\geq 2 \times$ upper limit of normal – ULN), and treatment sensitivity [19]. In acute leukemias, the most important seem to be the bone marrow involvement and high white blood counts ($\geq 100 \times 10^9/L$ or $<100 \times 10^9/L + LDH \geq 2 \times ULN$), while in CLL, treatment with venetoclax and lymph node ≥ 10 or ≥ 5 cm and absolute lymphocyte count $\geq 25 \times 10^9/L$ and elevated uric acid and spleno- and hepatomegaly [19]. Therefore,

Fig. 3. TLS risk stratification for hemato-oncologic malignancies in adults [20, 80]. The dotted lines indicate the final TLS risk adjustment based on renal function and baseline uric acid, phosphate, and potassium serum concentrations. TLS, tumor lysis syndrome; CLL, chronic lymphocytic leukemia; WBC, white blood cells; AML, acute myeloid leukemia; LDH, lactate dehydrogenase; ULN, upper limit of normal.

before TLS risk stratification, every patient with CLL or non-Hodgkin lymphoma should have a staging computed tomography of the chest, abdomen, and pelvis.

The intermediate-risk category for TLS includes the same (1) non-Hodgkin lymphomas, but in early stages, not bulky or with low proliferation potential (LDH < 2 × ULN), (2) acute leukemias with lower WBC counts, and (3) CLL treated with fludarabine, rituximab or lenalidomide, or treated with venetoclax and with lymph node ≥ 5 cm, or with absolute lymphocyte count ≥ 25 × 10⁹/L, or CLL with WBC ≥ 50 × 10⁹/L. Additionally, there have been some classified highly chemotherapy-sensitive neoplasms such as neuroblastoma, germ cell tumors, and small-cell lung cancer, when bulky and in advanced stages [20].

All these factors must be interpreted together (Fig. 3). Keeping in mind the crucial role of preserved renal function, it is logical that renal dysfunction/involvement automatically upgrades the risk category.

Therapy-Related Factors

During the last twenty years, particularly the last decade, the expanding knowledge of cancer immune evasion mechanisms and host-tumor interactions has significantly changed our therapeutic strategies in hemato-oncology [21–25]. Several novel targeted molecular and immune cell-based agents are now available, usually to be used in combination with conventional cytotoxic agents [26]. Thereby, more neoplasms with a low proliferation rate, often refractory to the traditional cytotoxic chemotherapies, became responsive to much more effective new anticancer therapies. This concerns some solid tumors (pulmonary, gynecologic, gastrointestinal, neurologic, and sarcomas, especially advanced and metastatic); however, the most dramatic changes have been observed in CLL and small lymphocytic lymphoma (SLL) [3, 18, 27]. The introduction of small molecule inhibitors has dramatically transformed this otherwise rather indolent hematological malignancy into a disease with a clinically significant risk for TLS, concerning 10–18% of patients in early phase studies [19].

In general, the treatment of CLL/SLL targets 3 major cell pathways involved in the pathogenesis of B-cell proliferation: Bruton tyrosine kinase (BTK), phosphoinositide-3-kinase (PI3K), and the B-cell lymphoma-2 receptor (BCL-2). According to the current guidelines, targeted therapy with BTK inhibitors (ibrutinib) and BCL-2 inhibitor, venetoclax, is the preferred first-line treatment of all patients with CLL [28]. Fludarabine, cyclophosphamide, and rituximab are preferred for patients <65 years with untreated *IGHV*-mutated CLL. BTK inhibitors (ibrutinib and acalabrutinib), PI3K inhibitors (idelalisib, alt. with rituximab, and duvelisib), and venetoclax ± rituximab remain effective treatment options for relapsed/refractory CLL/SLL.

BCL-2 Inhibitors

BCL-2-type proteins are key molecules in cell regulatory pathways for apoptosis. The high efficacy of the first BCL-2 inhibitor, venetoclax, used in CLL, seems to be due to the pathophysiology of the disease, which is characterized by an overexpression of BCL-2 receptors [29]. In early clinical studies, the treatment with venetoclax was associated with the significant risk of TLS (8.3 and 8.9% of studied patients), with 2 TLS-associated fatalities, which led to a suspension of the trials [30, 31]. This resulted in the development of effective TLS mitigation strategies with step-wise dosing (dose ramp-up) of the drug, lowering WBC below $25 \times 10^9/L$ with hydroxyurea before starting treatment with venetoclax or chemoimmunotherapy (BTK inhibitor and CD20 monoclonal antibody) [19, 32]. The debulking strategies, together with adequate hydration and more careful biochemical monitoring, resulted in a considerable decrease in TLS risk to approximately 1–3.8% and clinical TLS to <1% [19, 29, 33–36]. In other hematological diseases (multiple myeloma and AML), TLS is uncommon [37–43].

BTK Inhibitors

BTK inhibitors are the other agents currently used in CLL, targeting B-cell receptor signaling pathways. They may be given as a monotherapy or concurrently with venetoclax since there is a marked synergy between these drugs and their complementary activity. Since BTK inhibitors are highly active in treating and shrinking nodal disease and BCL-2 inhibitors are highly effective at clearing blood and bone marrow, their combination and therapeutic sequencing may permit treatment of shorter duration and lower intensity than chemotherapy, while still preserving the disease-control benefits [28, 29, 44]. The results of the phase II CAPTIVATE study, in which the BTK inhibitor, ibrutinib, was given with venetoclax as frontline therapy, are encouraging for both efficacy and safety [44]. There were 3 cases of laboratory TLS and no clinical manifestation. Moreover, the ibrutinib lead-in period resulted in a considerable tumor bulk reduction, with downgrading of the TLS risk category in 80% of

the high-risk patients and 48% of the medium-risk patients [36]. Similarly, promising results were achieved in the CLARITY study, in which the ibrutinib-venetoclax combination was given to patients with relapsed/refractory CLL, with TLS 2% (one of 50 patients) [35].

PI3K Inhibitors

Similar to BTK inhibitors, PI3K inhibitors block B-cell receptor signaling, interfering with several pathways required for leukemia cell survival. Two of them, idelalisib and duvelisib, have been approved by the FDA to treat relapsed/refractory CLL and SLL based on the results of the phase III randomized DUO study and the DYNAMO study [45–47]. There were single 3 case reports of TLS in patients treated with idelalisib, but no laboratory or clinical TLS was observed in major clinical trials [46–48].

CDK Inhibitors

The regulatory role of cyclin-dependent kinases (CDKs) in the transition of cell steps that are necessary for its proliferation makes these enzymes a natural target for cancer therapy. The first CDK inhibitors to enter clinical trials were alvociclib and dinaciclib, given in high-risk CCL, acute leukemias, multiple myeloma, lymphomas, and some tumors. Both drugs exerted nonselective, inhibitory effects on a wide range of CKDs, including CKD9, which is implicated in CLL. In phase I and II trials, the major issue of these drugs was their toxicity profile to healthy cells, which led to severe side effects with a strikingly high incidence of TLS, reaching 40–50% patients for laboratory TLS and 15% for clinical TLS, with many of them requiring immediate hemodialysis [49–53]. Although a combination with other anticancer drugs was shown to mitigate their toxicity [54], both drugs were abandoned and replaced by selective CDK4/6 inhibitors palbociclib, ribociclib, and abemaciclib, with more favorable safety profile with no TLS syndrome reported. These drugs are FDA approved as a frontline treatment of breast cancer [55].

Proteasome Inhibitors

Proteasome inhibitors (bortezomib, oprozomib, carfilzomib, and ixazomib) block the function of the proteasome, the garbage disposal system of the cell, from the degradation of excess proteins, which in consequence build up in a cell leading to its death. They are an important class of drugs for the treatment of multiple myeloma and certain types of lymphoma, which generate a lot of additional proteins. Generally, the risk of TLS in multiple myeloma is low, given the disease's low proliferation rate. However, after the introduction of proteasome inhibitors, an increasing frequency of TLS has been reported, with an incidence of 1.4–5% for bortezomib, 0.4–4.3% for carfilzomib, and 2.4% for oprozomib [9, 56–58].

Monoclonal Antibodies

The rate of TLS after treatment with first-generation anti-CD20 monoclonal antibody rituximab is low, in case reports or case series [56, 59]. Among the next-generations of these drugs, obinutuzumab, used in combination with chlorambucil in patients with relapsed/refractory CLL, was associated with 4.8% incidence of TLS in phase 1 and 2 studies [60] and with 4.3% in a recent phase 3 ILLUMINATE study [61].

Proapoptotic Agents

The rate of TLS with a proapoptotic agent, lenalidomide, seems to be low (0–4%), particularly when used in patients with relapsed/refractory CLL (<5%) [3, 17, 62, 63].

CAR T-Cell Therapy

The therapy uses the patient's cells, which are ex vivo genetically engineered to produce specific chimeric antigen receptors (CARs) on their surface, to direct them against the leukemic

cells. Then, these modified cells are multiplied and infused back to the patient as therapy. TLS has been described in patients with acute and chronic hematologic malignancies after CAR T-cell therapy; however, the true incidence may be not yet known being overshadowed by coincident cytokine release syndrome [64–66]. In 2 large clinical studies conducted in adult patients with refractory large B-cell lymphoma, one with tisagenlecleucel and a second with axicabtagene ciloleucel CAR T-cell therapy, no cases of TLS were reported [67, 68]. However, in the recent phase 2, 25-center study, a global study of tisagenlecleucel in children and young adults with relapsed or refractory B-cell ALL, TLS occurred in 3 of 75 patients (4%) [65]. Therefore, regular – daily if possible – inpatient monitoring and TLS prophylaxis are recommended for patients with a high disease burden or elevated serum uric acid [69].

Immune Checkpoint Inhibitors

Immune checkpoint inhibitors are monoclonal antibodies that enhance tumor killing by T cells by releasing a natural brake (checkpoint proteins) on patient's immune system so that the patient's T cells could recognize and kill tumor cells. In patients treated with immune checkpoint inhibitors, TLS seems to be a rare complication, but it can be life threatening. Cordrey and Wang [70], in their systemic review of the literature, identified only 5 publications (4 case reports and 1 phase I clinical trial report) with a total of 6 cases of TLS after treatment with the immune checkpoint inhibitors. The median time from treatment to TLS was 14 days, with a range of 2 to 33 days. Four of these patients died; all of them had extensive liver metastases. The authors postulate the lack of awareness of TLS risk, together with its delayed occurrence in solid tumors, may contribute to the higher mortality as well as to the underdiagnosing and underreporting.

Prophylactic Measures

The prophylactic measures are vigorous IV hydration, urate-lowering therapy, avoidance of exogenous potassium and phosphate, and – in high-risk cases – considering cyto reduction before the start of the aggressive agent or a gradual escalation of its dose. Prophylactic use of phosphate binders or potassium binding resins is not recommended while avoiding additive potassium in intravenous fluids seems reasonable.

Intravenous Fluid Expansion

Patients should be instructed to drink 1.5–2.0 L of water daily starting 2 days before and throughout the dose-titration phase. Intravenous fluids should be administered as indicated based on overall risk of TLS or for those who cannot maintain an adequate level of oral hydration. It should be started at least 24 h before the anticancer drug dosing, provided that the patient is well hydrated, and continued for 24–48 h after completion of the therapy. The infusion rates should be high enough to keep urinary output >100 mL/h, with daily urine volumes of at least 3 L. In patients with evidence of fluid overload, or with insufficient diuresis despite well hydration, the loop diuretics may be considered. Thiazide diuretics are contraindicated since they increase uric acid levels and interact with allopurinol. In the era of rasburicase, urinary alkalization is no longer recommended since it may cause heavy calcium phosphate precipitation [17, 71].

Urate-Lowering Therapy

In the aforementioned guidelines, 2 uric acid-decreasing agents, the conventional xanthine oxidase inhibitor allopurinol and the recombinant uricase rasburicase, are recommended for the prophylaxis and management of TLS. Allopurinol is used to treat patients at low and intermediate risk of TLS, and rasburicase for patients with high risk, renal failure, and those with already existing TLS [17, 72].

Allopurinol

Allopurinol, a xanthine oxidase inhibitor, blocks the conversion of nucleic acids released from cancer cells to hypoxanthine to xanthine and xanthine to uric acid (Fig. 3), which are much more easily cleared by the kidney. Since it does not remove the existing uric acid, it usually takes a few days to reduce its concentration. Therefore, it is recommended that the treatment should be started 2–3 days before chemotherapy and continued at least for 10–14 days or until the signs of massive tumor lysis are absent [27, 73]. Typically, the drug is given orally at a dose of 600–800 mg daily; if necessary, it can also be given intravenously. Allopurinol is excreted by the kidney, which imposes the dose reduction in renal dysfunction and significantly limits the number of patients who may benefit from the treatment. The dose should also be reduced or the drug avoided in patients concomitantly treated with azathioprine, cyclophosphamide, or 6-mercaptopurine since it can potentiate their cytotoxic effects. The adverse effects are usually mild and include pruritic rash, diarrhea, leukopenia, and thrombocytopenia, occurring in 3–5% of the patients; however, more severe hypersensitivity skin reactions, acute interstitial nephritis, and xanthine nephropathy have been described.

Febuxostat

Recently, a novel potent nonpurine xanthine oxidase inhibitor, febuxostat, the medication approved for gout treatment, is being tested in preventing TLS. Since the drug is metabolized via glucuronidation and oxidation, with only 1–6% of the dose being excreted unchanged via the kidneys, no dose adjustment is necessary for patients with mild or moderate renal impairment [74]. The first studies demonstrated its efficacy in uric acid reduction and suggested that febuxostat may serve as an alternative to allopurinol in patients with renal dysfunction, allopurinol intolerance, or allopurinol resistance [75, 76]. The drug is usually started 24 h before chemotherapy and discontinued after the risk of TLS is minimal or absent. In a recent meta-analysis which included 6 studies with a total of 659 patients, febuxostat achieved a similar response rate, TLS incidence, and the rate of adverse events when compared to allopurinol [77]. However, the drug is not free from side effects, the most serious being Stevens-Johnson syndrome, anaphylaxis, and, as suggested by a recent safety trial, an increased risk of cardiac and all-cause mortality [78]. On this basis, in 2019, the FDA released a boxed warning limiting febuxostat use to the patients with hyperuricemia who cannot tolerate allopurinol in a setting in which rasburicase is not available or is contraindicated [79, 80].

Rasburicase

Rasburicase is a recombinant urate oxidase produced in genetically modified *Saccharomyces cerevisiae*. It decreases serum uric acid concentrations by converting it into an inactive metabolite, allantoin, easily soluble in water and excreted in the urine. Unlike allopurinol, its action is immediate, with a rapid decrease in serum acid concentration. In contrast to allopurinol, there is no need for rasburicase dose adjustment in patients with renal dysfunction. It is noteworthy that since rasburicase degrades uric acid in blood and plasma at room temperature, to avoid false results, the blood samples must be collected in pre-chilled tubes and immediately sent to the laboratory on ice, with the assay performed in 4 h of collection.

In several clinical trials, rasburicase has been shown to be effective and safe in both adults and children. The drug should be administered 4–24 h before starting chemotherapy. The labeled dose is 0.2 mg/kg, daily given as a 30-min IV infusion, for up to 5 days [72]; however, in patients with low-intermediate risk of TLS, the smaller doses (0.1–0.15 mg/kg) were demonstrated to be also efficient, allowing for substantial cost reduction [81]. Alternatively, for patients with the low to moderate risk, a single fixed (3, 4.5, 6, or 7.5 mg) or weight-based (0.15–0.20 mg/kg) dose regimen has been proposed, and its efficacy is demonstrated [82–88]. A systematic review and meta-analysis of 19 studies by Yu et al. [89] revealed that

Table 1. Recommended TLS prophylaxis based on tumor burden in patients with CLL and SLL [95]

Category of tumor burden		Prophylaxis		Blood chemistry monitoring ^c
		hydration	anti-hyperuricemics	setting and frequency of assessments
Low	All lymph nodes <5 cm and ALC <25 ×10 ⁹ /L	Oral (1.5–2 L) ^a	Allopurinol ^b	Outpatient For first dose of 20 and 50 mg: predose, 6–8 and 24 h For subsequent ramp-up doses: predose
Medium	Any lymph node 5 to <10 cm or ALC ≥25 ×10 ⁹ /L	Oral (1.5–2 L) and consider additional IV	Allopurinol ^b	Outpatient For first dose of 20 and 50 mg: predose, 6–8 and 24 h For subsequent ramp-up doses: predose For first dose of 20 and 50 mg: consider hospitalization for patients with CLcr <80 mL/min: see below for monitoring in hospital
High	Any lymph node ≥10 cm or ALC ≥25 ×10 ⁹ /L and any lymph node ≥5 cm	Oral (1.5–2 L) and IV (150–200 mL/h as tolerated)	Allopurinol ^b : consider rasburicase if baseline uric acid is elevated	In hospital For first dose of 20 and 50 mg: predose, 4, 8, 12, and 24 h Outpatient For subsequent ramp-up dose: predose, 6–8 and 24 h

CLL, chronic lymphocytic leukemia; SLL, small lymphocytic lymphoma; TLS, tumor lysis syndrome; ALC, absolute lymphocyte count; CLcr, creatinine clearance. ^a Administer IV hydration for any patient who cannot tolerate oral hydration. ^b Start allopurinol or febuxostat 2–3 days prior to initiation of venetoclax. ^c Evaluate blood chemistries (potassium, uric acid, phosphorus, calcium, and creatinine); review in real time. For patients at risk of TLS, monitor blood chemistries at 6 to 8 h and at 24 h at each subsequent ramp-up dose.

single doses of rasburicase: 6 mg for adults and 1.5 and 0.15 mg/kg for children, were sufficient to normalize and sustain lower uric acid and creatinine levels in adults with TLS. According to these authors, the 3- and 4.5-mg single doses can be considered if the baseline uric acid level is <12 mg/dL. In patients treated with the single-dose regimen, a reassessment of clinical and biochemical parameters is necessary, with repeating the dose if required [3, 89]. Cortes et al. [90] demonstrated that sequential therapy with rasburicase followed by allopurinol was similarly effective and may be a reasonable and cost-effective approach with similar efficacy in adults with hyperuricemia or at high risk for TLS.

One of the important factors limiting use of rasburicase is the considerable cost of the drug. However, in a retrospective study, Cairo et al. [91] compared reductions in uric acid, length of ICU, hospital stay, and hospitalization costs in 26 rasburicase-treated and 104 allopurinol-treated patients with TLS (matched in the ratio 1:4). Length of ICU and hospital stay was 2.5 and 5 days less for the rasburicase group ($p < 0.0001$ and $p = 0.02$, respectively). Total treatment costs per patient ($\Delta 20,038\$$; $p < 0.02$) as well as cost per percentage of uric acid reduction ($\$3,899$ vs. $\$16,894$; $p < 0.001$) occurred to be significantly lower for patients treated with rasburicase than for those treated with allopurinol.

Although generally very well tolerated, rasburicase may cause serious and fatal adverse events, such as hypersensitivity reactions, including anaphylaxis, as well as severe oxidative hemolytic anemia and methemoglobinemia in patients with glucose-6-phosphate dehydrogenase deficiency [92–94]. For that reason, it carries the FDA boxed warning to alert the physician to these risks and take all appropriate precautions when introducing the drug [92]. Rasburicase is contradicted in patients with glucose-6-phosphate dehydrogenase deficiency. Therefore, the patients at risk (males of African, Asian, and Mediterranean descent) should be screened for this genetic abnormality before its administration [93]. The repeated exposure to rasburicase should be avoided since anaphylaxis after the second course of rasburicase appears to occur more frequently [94]. In any patient developing clinical symptoms of hypersensitivity, the drug should be immediately and permanently discontinued [92].

Taking into account the aforementioned risks, there is a need for clear recommendations for its use in the setting of TLS. According to the US Prescribing Information (USPI), rasburicase is recommended in patients with high risk of TLS, particularly those with elevated baseline uric acid or in already existing syndrome (Table 1) [95]. It seems also reasonable to use it in patients with high or even intermediate TLS risk and renal or heart failure who cannot tolerate aggressive hydration.

Monitoring Approach

In all patients who are beginning anticancer therapy, several laboratory and clinical parameters should be carefully monitored. These include serum potassium, uric acid, phosphate, calcium, creatinine concentration, and LDH activity, as well as diuresis and fluid balance, which should be assessed on an ongoing basis. The frequency of laboratory parameter monitoring depends on the risk of TLS. While in low-risk patients, it can be done once daily, those at intermediate risk should undergo laboratory monitoring every 8–12 h, and those at high risk, every 4–6 h [3]. It is recommended to start the monitoring before initiation of chemotherapy and continue as long as the patient is at risk for TLS, which depends on the therapeutic regimen [3].

Management of Established TLS

Hyperphosphatemia

In some patients, other factors besides hyperuricemia may play a key role in the development of TLS and AKI, and the urate-lowering therapy may not be sufficient as a preventive measure. The second most common metabolic disorder responsible for AKI, which cannot be underestimated, is hyperphosphatemia. Malignant cells contain up to 4 times more phosphate than normal cells and this increases further in hyperproliferative states such as blast crisis [96].

Phosphate-induced nephropathy may be aggravated when urinary alkalization is used, as high urine pH favors precipitation of calcium phosphate in the renal tubules. In a multicenter prospective French study by Darmon et al. [97], which enrolled 153 high-risk patients, TLS developed in 30.7% of cases (in 11.1% laboratory and 19.6% clinical from), despite urate-lowering treatment. In a logistic regression model, the serum phosphate concentration occurred to be the main risk factor associated with clinical TLS and AKI, with OR 5.3; 95% CI: 1.5–18.3 (per mmol/L). The authors stressed the role of acute phosphate nephropathy in AKI in a setting of TLS, which in some cases may be overlooked, especially in the light of current guidelines focused on the antiuricemic agents [97].

Therefore, the treatment of hyperphosphatemia cannot be underestimated and should be started immediately, with phosphate intake restriction and elimination from IV solutions, avoidance of bicarbonates, and use of oral noncalcium phosphate binders. For patients with severe acute serum phosphate increase, the prophylactic intensive care unit admission and the consideration of early institution of renal replacement therapy (RRT) seem reasonable, to prevent disseminated metastatic calcium deposition.

Hyperkalemia

Hyperkalemia is the most life-threatening abnormality in TLS; therefore, it must be aggressively treated. It may be aggravated by metabolic acidosis. In every patient with hyperkalemia, continuous cardiac rhythm monitoring, as well as an immediate nephrology consultation, is recommended, and urgent hemodialysis should be considered. In case of emergency (serum potassium >6.5 mmol/L, cardiac conduction abnormalities, arrhythmia, lengthening of the PR interval and widening of QRS, muscle weakness, or paralysis), while waiting for

hemodialysis, the rapidly acting therapies should be administered. These consist of IV infusion of 10% dextrose with rapid-acting insulin, to drive potassium into the cells, and IV calcium chlorate or gluconate to antagonize the membrane actions of hyperkalemia. If there is a risk of a longer delay before the dialysis is started, we administer oral gastrointestinal sodium-potassium exchange resins.

Hypocalcemia

Asymptomatic hypocalcemia often resolves as serum phosphate concentration is corrected, and the treatment, which may aggravate metastatic calcifications, is not recommended. Symptomatic patients should be treated with calcium at the lowest doses required to relieve symptoms [17, 80, 81].

Renal Replacement Therapy

In patients with a high risk of TLS, cytotoxic chemotherapy should be given in the facility with ready access to RRT and a treatment plan discussed with the nephrology team [81]. It must be remembered that in TLS, the threshold for RRT initiation may be lower than in other clinical situations, for 3 reasons. First is that the process of the cell break down is still ongoing and one cannot predict rapid increases in serum electrolytes in the individual patients, particularly in those with kidney dysfunction and oliguria. Secondly, early institution of RRT interrupts the pathological cascade with avoidance of life-threatening complications. Last but not least, it may prevent irreversible kidney injury. Early intervention is particularly favored in patients with congestive heart failure who cannot tolerate large fluid volumes. TLS in end-stage renal disease patients on dialysis seems to be extremely rare and we have found only 1 case report in the literature [98]. Therefore, no guidelines for optimal therapy in this population are available.

The choice of the RRT technique depends on the laboratory data and the malignant cell turnover rate as well as the clinical condition of the patient, volume status, hemodynamics, degree of impairment of other organs, and nutritional support. Intermittent hemodialysis is preferred in patients with severe hyperkalemia and severe hyperuricemia. In critically ill, continuous veno-venous hemofiltration, continuous veno-venous hemodialysis, or sustained low-efficiency daily dialysis seem to be a reasonable choice since they offer greater hemodynamic stability and better volume control, without the rebound hyperphosphatemia and hyperkalemia [99, 100]. For patients with severe hyperphosphatemia, continuous veno-venous hemodiafiltration has been proved as the most effective method of phosphate control [100, 101]. Peritoneal dialysis is not recommended for the treatment of TLS.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

J.M.R. and J.M.: design of the study, manuscript preparation, and final approval; J.M.R.: preparation of figures.

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