

Etiology and Management of Tumor Lysis Syndrome in Patients with Chronic Lymphocytic Leukemia

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Abstract: In the past few years, the number of effective treatment options for patients with chronic lymphocytic leukemia (CLL) has increased substantially. Purine analogs, bendamustine, monoclonal antibodies, and immunomodulatory drugs have shown higher response rates than previously achieved with standard CLL treatments such as alkylating agents. However, a consequence is that increased rates of tumor-cell killing may be accompanied by adverse secondary effects. One well-known consequence of rapid and massive cell killing is a group of metabolic disruptions collectively known as tumor lysis syndrome (TLS). TLS can be life threatening or fatal when unrecognized and/or untreated, and may cause delays in treatment of the underlying disease. It is important to be aware of patient risk factors, prophylactic measures, diagnostic criteria, and treatment for TLS. This review discusses the relevance of TLS to CLL treatment and provides guidelines for diagnosis, prevention, and treatment of TLS in patients being treated for CLL.

Introduction

Description of Tumor Lysis Syndrome

Tumor lysis syndrome (TLS) is characterized by an array of metabolic imbalances that develop in patients with cancer after the onset of chemotherapy treatment or, less often, prior to treatment. TLS has been reported most often in patients suffering from malignancies with a high rate of proliferation, especially cancers with a high response rate and rapid responses to cytotoxic therapy. These include aggressive non-Hodgkin lymphoma, notably diffuse large B-cell lymphoma, lymphoblastic lymphoma, and Burkitt lymphoma; acute and chronic leukemias; and, less often, bulky solid tumors. The characteristic laboratory abnormalities associated with TLS are hyperkalemia, hyperphosphatemia, hypocalcemia and hyperuricemia, which may be followed by impairment of kidney function. The pathophysiology of TLS is complex and may affect many organs (Figure 1).¹ The clinical consequences of TLS include cardiac dysrhythmias, seizures, diarrhea, nausea, vomiting, mental confusion or delirium, edema, fluid overload, congestive heart

Keywords

Tumor lysis syndrome, chronic lymphocytic leukemia, immunomodulatory drugs

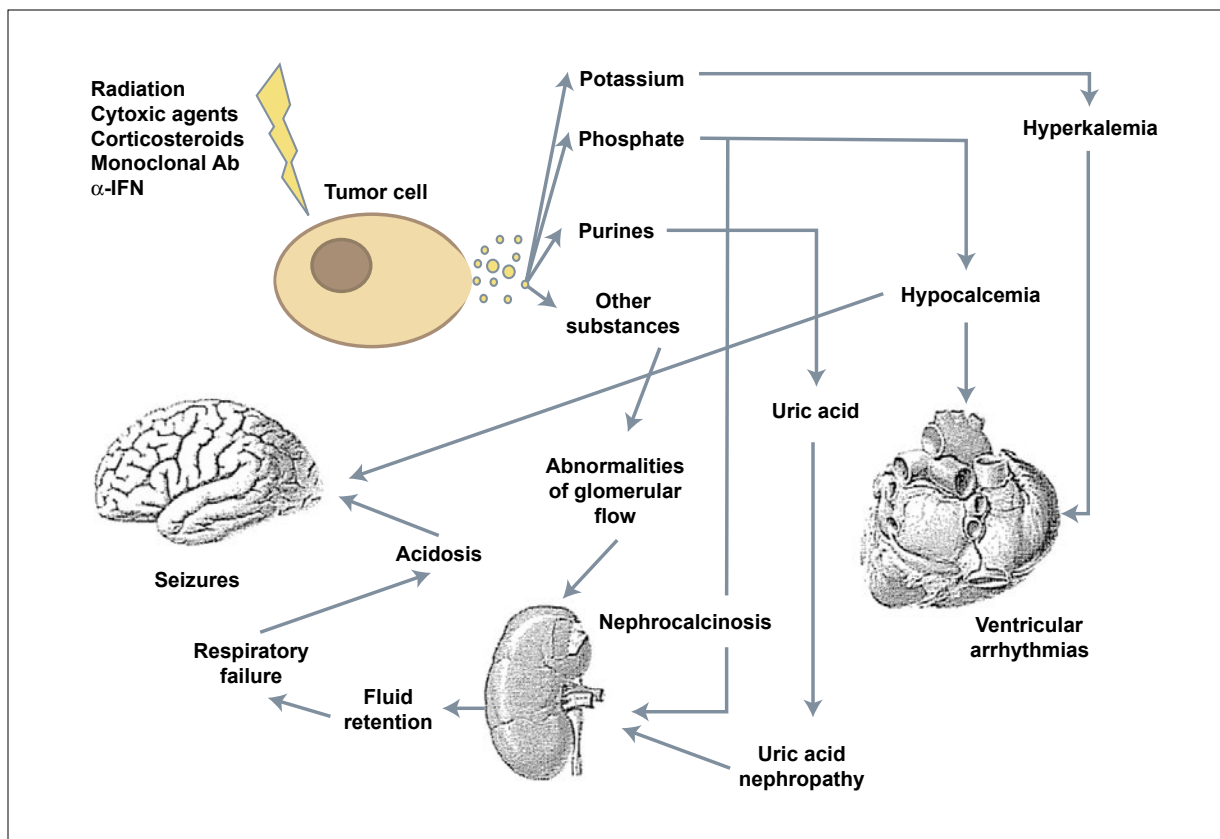


Figure 1. The pathophysiology of tumor lysis syndrome.¹

Ab=antibody; α-IFN=interferon α.

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failure, hypotension, muscle cramps or weakness, fainting, renal failure and potential sudden death.¹⁻³

Causes of TLS

Following the administration of therapy, malignant cells are killed rapidly, releasing into the circulation large amounts of intracellular components including nucleic acids, phosphorus, potassium, proteins, and other intracellular anions and cations. The nucleic acids that are released into the circulation are metabolized further into uric acid which, due to its poor solubility, can overload the processing ability of the kidneys, leading to hyperuricemia and possibly renal failure. In conjunction, high levels of potassium from lysed tumor cells can further overwhelm the kidneys, already compromised by uricemia, leading to the rapid development of hyperkalemia that can cause cardiac arrhythmias. The hypocalcemia observed as part of TLS is secondary to hyperphosphatemia, and is due to the formation of calcium phosphate crystals in renal tubules that can result in obstructive nephropathy.^{2,3} In

the majority of cases, TLS occurs within 2–3 days of initiation of chemotherapy; however, in some cases the occurrence may be delayed, even rarely occurring during the second cycle of therapy.

Diagnosis of TLS

A distinction needs to be made between laboratory TLS (LTLS) and clinical TLS (CTLs) because only a minority of patients with LTLS develops CTLs. Indeed, in patients devoid of clinical symptoms, TLS may go unnoticed. Regular monitoring of patients will aid timely recognition of LTLS, and is recommended for all patients who undergo treatment for high-risk malignancies, including specific types of patients with CLL.

Cairo and Bishop refined previous TLS classification systems to permit a more accurate diagnosis and grading of TLS in a clinical setting.² The classification is three-tiered and includes patients with no TLS, those with LTLS, and those with CTLs.

Table 1. Cairo & Bishop Grading Classification of Tumor Lysis Syndrome²

	Grade 0*	Grade I	Grade II	Grade III	Grade IV	Grade V
LTLS	-	+	+	+	+	+
Creatinine ^{†‡}	≤1.5 × ULN	1.5 × ULN	>1.5–3.0 × ULN	>3.0–6.0 × ULN	>6.0 × ULN	Death [§]
Cardiac arrhythmia [‡]	None	Intervention not indicated	Non-urgent medical intervention indicated	Symptomatic and incompletely controlled medically, or controlled with a device (e.g. defibrillator)	Life-threatening (e.g. arrhythmia associated with chronic heart failure, hypotension, syncope, shock)	Death [§]
Seizure [‡]	None	–	One brief generalized seizure; seizure(s) well controlled by anti-convulsants or infrequent focal motor seizures not interfering with activities of daily living	Seizures in which consciousness is altered; poorly controlled seizure disorder; with breakthrough generalized seizures despite medical intervention	Seizures of any kind which are prolonged, repetitive or difficult to control (e.g. status epilepticus, intractable epilepsy)	Death [§]

LTLS=laboratory tumor lysis syndrome; ULN=upper limit of normal.

Note: Clinical tumor lysis syndrome (CTLS) requires one or more clinical manifestations along with criteria for LTLS. Maximal CTLS manifestation (renal, cardiac, neuro) defines the grade.

*No LTLS.

[†]Creatinine levels: patients will be considered to have elevated creatinine if their serum creatinine is 1.5 times greater than the institutional ULN but below age/sex defined ULN. If not specified by an institution, age/sex ULN creatinine may be defined as: aged >1 to <12 years, both male and female, 61.6 μmol/L; aged ≥12 to <16 years, both male and female, 88 μmol/L; aged ≥16 years female 105.6 μmol/L and ≥16 years male 114.4 μmol/L.

[‡]Not directly or probably attributable to a therapeutic agent (e.g. rise in creatinine after amphotericin administration).

[§]Attributed probably or definitely to CTLS.

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LTLS

According to the definition proposed by Cairo and Bishop,² LTLS is characterized by the presence of 2 or more of the following serum levels within 3 days before or 7 days after the initiation of chemotherapy, assuming the patient receives adequate hydration and a hypo-uricemic agent during treatment.

- Uric acid levels of ≥476 mol/L or a 25% increase from baseline
- Potassium levels of ≥6.0 mmol/L or 25% increase from baseline
- Phosphorous levels of ≥2.1 mmol/L in children, or ≥1.45 mmol/L in adults, or 25% increase from baseline
- Calcium levels of ≤1.75 mmol/L or 25% decrease from baseline

CTLS

In general, CTLS can be diagnosed in the presence of laboratory evidence of metabolic changes that meet the definition for LTLS, with a significant level of clinical toxicity that requires intervention. CTLS is defined by evidence of renal insufficiency (creatinine level of at least 1.5 times the upper limit of normal [ULN]), potentially fatal cardiac arrhythmia and/or seizures that are not directly attributable to a therapeutic agent. CTLS is further graded by the severity of the clinical manifestation (Table 1).² The presence of CTLS necessitates aggressive clinical intervention.

TLS Risk Factors

Major risk factors for TLS include high tumor burden, high rate of proliferation, and disease that is highly responsive to therapy.^{2,4} Other factors include pre-existing

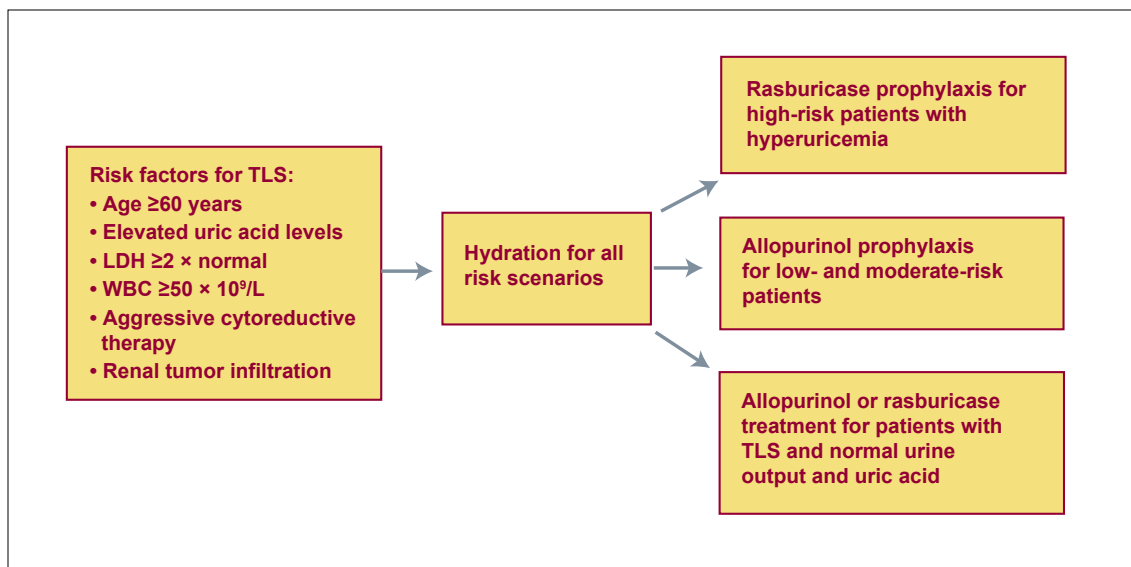


Figure 2. Recommendations for hyperuricemia agents.⁵

LDH=lactase dehydrogenase; TLS=tumor lysis syndrome; WBC=white blood cell count.

hyperuricemia, elevated lactate dehydrogenase (LDH), renal dysfunction, age 60 years or older, and dehydration.^{2,5} There are no known risk factors related to sex or ethnicity.¹ Factors related to a patient’s current therapy may also predispose them to TLS. These include the administration of supplements that contain potassium and phosphorus, intravenous or enteral nutritional components, medications that are toxic to the kidney, and potassium-sparing diuretics.

Prophylaxis and treatment of TLS should be adapted to the risk of the patient for developing TLS and/or the presence of hyperuricemia when the patient is suffering TLS. Recently, an expert panel was convened to develop a medical decision model to identify various risk groups and to recommend preventative or therapeutic approaches for each risk group (Figure 2).⁵

Treatment-related TLS in Patients with Chronic Lymphocytic Leukemia

Chronic Lymphocytic Leukemia

Chronic lymphocytic leukemia (CLL) is the most common form of leukemia in western countries with 15,110 new cases of CLL projected to be diagnosed in the United States during 2008, and about 4,390 patients expected to die from the disease.⁶ CLL is characterized by the accumulation of morphologically mature monoclonal B-lymphocytes in the blood bone marrow, lymph nodes, spleen, and liver.⁷ It occurs primarily in older adults, with more than 50% of cases diagnosed in people over the age

of 70 years.⁸ About half of all patients are asymptomatic at diagnosis, which is most often identified incidentally by an elevated lymphocyte count during routine blood tests. Patients may also present with lymphadenopathy and, upon further evaluation, are noted to have splenomegaly, hepatomegaly, anemia, or thrombocytopenia. A smaller number of patients experience skin infiltrations, autoimmune hemolytic anemia or thrombocytopenia, and hypogammaglobulinemia.

The availability of new therapies appears to have prolonged the survival of patients with CLL^{9,10}; nevertheless, a cure is still lacking.⁸ Effective treatments improve response rates in CLL, but may also result in TLS as a result of the rapid killing of malignant cells. Fortunately, TLS prophylaxis options are available and should be considered in the context of treating CLL patients at high risk for developing TLS.

Occurrence of TLS in CLL Treatment

Fludarabine Several randomized trials have shown the benefit of single-agent, purine analog fludarabine compared with alkylating agent-based combinations with regard to response rate and remission duration. A randomized trial by Rai and colleagues¹¹ demonstrated an overall response rate of 63% with 20% complete remissions in newly diagnosed CLL patients, compared with an overall response rate of 37% with chlorambucil with 4% complete remissions. The median time-to-progression of disease in patients treated with fludarabine was 20 months compared with 14 months

for chlorambucil. The median overall survival was 66 months and 56 months for fludarabine- and chlorambucil-treated groups, respectively.

In a retrospective study of patients with advanced CLL who received single-agent fludarabine therapy, TLS was suspected in 26 (0.42%) of 6,137 patients.¹² Of the patients included in the analysis, 90% had high-risk disease and 60% had received TLS prophylaxis (allopurinol and/or hydration). In the study, there was no evidence that preventive measures were successful. TLS developed on approximately day 7 and was fatal in 20% of cases. A more recent report cited a CLL patient treated with fludarabine who developed TLS twice after oral fludarabine treatments; in each case the TLS developed more than 2 weeks after initiation of therapy.¹³

Bendamustine Bendamustine (Treanda, Cephalon) is a cytotoxic agent with both alkylating and antimetabolic properties. As a result of its unique mechanism of action, bendamustine has activity in lymphomas that are resistant to alkylating agents and other drugs.¹⁴ In a recent study, 305 previously untreated CLL patients were treated with either bendamustine (156 patients) or chlorambucil (149 patients). The patients treated with bendamustine achieved an overall remission rate of 67% compared to 30% for chlorambucil-treated patients ($P > .0001$).¹⁵ Superior activity over chlorambucil led to approval by the United States Food and Drug Administration for the treatment of CLL. The incidence of TLS with bendamustine is rare, with only 1% of patients receiving bendamustine in this study experiencing this complication. Following the first course of bendamustine in a phase I/II trial for pretreated CLL patients, a patient with pre-existing renal dysfunction and hyperuricemia experienced massive TLS.¹⁶

Rituximab Rituximab (Rituxan, Genentech), a chimeric anti-CD20 monoclonal antibody, has been used extensively in the treatment of CLL, although not yet approved for the indication. The administration of this antibody resulted in an overall response rate of approximately 10–15% in previously treated patients, but about 50% when used as the initial treatment for the disease.^{17–19} Rituximab in combination with fludarabine (FR) has demonstrated an overall response rate of 90% in newly diagnosed CLL patients.²⁰ In a retrospective analysis, it was suggested that FR may prolong progression-free survival and overall survival compared with single-agent fludarabine.⁹ Several single-arm studies showed that the combination of fludarabine with cyclophosphamide and rituximab (FCR) resulted in higher overall response rates than single-agent fludarabine (73–95% for FCR vs 60–75% for single-agent fludarabine in previously treated patients), with a trend towards prolonged overall

survival.^{10,21,22} Of note, direct confirmation of the benefit of FR or FCR compared with single-agent fludarabine from randomized trials is lacking. A recent retrospective analysis demonstrated that FCR had an improved clinical outcome without increased toxicity compared to fludarabine plus cyclophosphamide (FC) treatment. Previously untreated patients with CLL treated with FC exhibited overall and complete response rates of 87% and 39%, respectively, whereas the FCR group had 95% and 60%, respectively. The median progression-free survival for the FC group was 24 months, and has not been reached in the FCR group.²³ A recently completed multicenter trial of 817 patients with CLL has further confirmed that the FCR regimen significantly prolonged progression-free survival when compared with FC.²⁴

With more effective treatment comes the potential for a higher risk of TLS. The first case of rituximab-induced CTLS in a patient with CLL was described in a patient with a high CD20-positive lymphocyte count.²⁵ Following rituximab treatment, the patient's leukocyte and platelet counts dropped. The patient also exhibited a decrease in plasma prothrombin time and a rise in serum LDH activity. Complement factors were undetectable after 7 hours of initial treatment, suggesting a possible complement-mediated cell tumor lysis mechanism. Another case of rituximab-induced TLS has been reported in a patient who exhibited LTLS with elevated phosphate, uric acid, and LDH within 12 hours of administration of rituximab therapy. The patient eventually died of sepsis 7 days after rituximab treatment.²⁶ No cases of TLS have been reported with FR or FCR.

Of note, Byrd and colleagues described a syndrome associated with rituximab, which they labeled 'rapid tumor clearance'.²⁷ This syndrome differed from TLS as observed in CLL patients treated with fludarabine in that the characteristic features of TLS, such as severe electrolytic disturbances and renal failure, did not occur in patients with rapid tumor clearance. The authors suggested that the rapid tumor clearance syndrome in these patients may be the result of cytokine release due to tumor cell agglutination in the lung, liver, and spleen, followed by gradual tumor destruction by immune effector cells, which may have produced the transient laboratory findings of mild tumor destruction. A coagulopathy was also associated with this syndrome.

Flavopiridol Flavopiridol is a cyclin-dependent kinase inhibitor with activity against CLL in pre-clinical studies.²⁷ Despite an initial study using a 24- or 72-hour continuous infusion of flavopiridol failing to show clinical activity in CLL patients,^{28,29} an 11% response rate was observed when administering a 1-hour bolus infusion.²⁵ However, when using a 30-minute loading dose followed

by a 4-hour infusion, a partial response rate of 45% (no complete responses) was observed.³⁰

One unexpected result in the Byrd and colleagues³⁰ study was that hyperacute TLS was observed as the dose-limiting toxicity in 6 of 42 (14%) patients. Leukocyte count was a major risk factor for TLS, with 5 of the 6 patients who developed hyperacute TLS requiring dialysis with the first dose of flavopiridol and having a pretreatment leukocyte count of more than $200 \times 10^9/L$. Of 8 patients with high leukocyte counts, 5 (63%) developed TLS requiring dialysis, and of those with pretreatment leukocyte counts of less than $200 \times 10^9/L$, only 1 of 34 (3%) patients developed TLS requiring dialysis. In some of the patients requiring dialysis for their TLS, complete normalization of LDH levels did not occur until 2 weeks after therapy. Unfortunately, the TLS observed in this study was eventually fatal for some patients. As a result, the investigators have restricted this therapy to patients with a leukocyte count of less than $200 \times 10^9/L$.

Lenalidomide Lenalidomide (Revlimid, Celgene) is an oral immunomodulatory derivative of thalidomide (Thalomid, Celgene) with potent activity, but a toxicity profile that is different from the parent compound. Lenalidomide has immunomodulatory, antiangiogenic, antineoplastic, and anti-inflammatory effects.³¹

Chanan-Khan and coworkers were the first to report treating relapsed and refractory patients with CLL using single-agent lenalidomide.³² Lenalidomide was administered orally at 25 mg/day (days 1–21 of a 28-day cycle), and allopurinol prophylaxis was given for prevention of TLS. Lenalidomide treatment resulted in a response in 53% of patients, with 18% achieving a complete remission.³³ Of 45 patients enrolled, 2 experienced TLS on day 9 of the first treatment cycle, and 1 of these patients experienced a second episode of TLS at a lower dose (15 mg).^{32,33} Both of these patients had stage 3 or 4 bulky disease. Slow dose escalation resulted in improved tolerability and is suggested to be a better way of administering lenalidomide in this setting.³²

Ferrajoli and coauthors³⁴ investigated the efficacy and safety of a starting dose of 10 mg of lenalidomide (daily for 28 days) with escalation up to 25 mg in relapsed or refractory patients with CLL. The overall response rate was 31% including complete remission in 7% of patients. The median dose tolerated was 10 mg of lenalidomide, with 7% of patients tolerating 25 mg for at least 1 month. In this study there were no incidents of TLS in the 44 patients enrolled. Whether the absence of this toxicity reflects the lower dose used in this study is unclear.

A summary of the available data by the manufacturer shows that TLS has been observed in 7 of 260 (2.7%) CLL

patients treated with lenalidomide to date.³⁴ All 7 patients had onset of TLS during the first 15 days of treatment and were distinguishable from those who did not have TLS by the presence of bulky disease, moderate renal insufficiency, and increased uric acid levels prior to therapy.³⁵ Another case of TLS with lenalidomide treatment (25 mg), not included in the 260 patients mentioned previously, has been reported in a patient with bulky lymphadenopathy and a white blood cell count of $197,000/mm^3$ prior to therapy.³⁶ After omitting his steroid prophylaxis, this patient developed a syndrome with laboratory evidence of TLS.³⁷

Single-agent lenalidomide is currently being investigated in newly diagnosed patients. After a starting dose of 10 mg and further escalation to 25 mg, a patient developed acute TLS with renal failure and was removed from the study. The protocol was revised with a lower starting dose (2.5 mg) and a lower target dose (10 mg), slower dose escalation, and extended allopurinol TLS prophylaxis for at least 3 cycles. Preliminary data from 8 patients enrolled on the new protocol show a partial response in 75% of patients by the end of cycle 2 with a maximum dose of 5 mg, with no further occurrences of TLS.³⁷

These results confirm that a lower starting dose of 10 mg of lenalidomide and slow dose escalation together with adequate prophylaxis might help reduce the occurrence of TLS in patients with CLL.

Management of TLS

The successful management of acute TLS requires awareness of patient risk factors prior to treatment, identification of high-risk patients, aggressive prophylactic strategies to prevent the development of clinical manifestations of TLS, electrolyte monitoring during treatment, and rapid treatment of TLS by healthcare professionals properly trained in the management of TLS.

Prevention of TLS in CLL Patients

Monitoring By understanding the impact of risk factors on the development of TLS, and by timely recognition of TLS, life-threatening consequences can be prevented. Hospitalization may be considered for patients with very high white blood cell counts (eg, $>50,000/mm^3$) to ensure adequate hydration and careful monitoring. In patients with previous episodes of CTLS, it is recommended that nephrology consultation be obtained prior to therapy. In the event of overt uremic symptoms, dialysis must be initiated to prevent acute renal failure.³⁸ For patients treated as outpatients, the frequent monitoring of serum electrolytes and uric acid is recommended (eg, 3 times/week for the first 2 weeks and weekly thereafter).

Delay of CLL treatment In patients with CLL at high risk of developing TLS, the risks of delaying CLL treatment must be weighed against the risk of developing or exacerbating TLS.

Hydration Adequate hydration and diuresis (to be avoided in hypovolemic patients) are the first and most important steps in the prevention of TLS. Unless a patient has signs of acute renal dysfunction and oliguria, fluid volume should be maintained by intravenous fluid administration at greater than or equal to 3,000 mL/m²/24 hours for 2 days prior and 2–3 days following treatment to maintain a urine output of more than 100 cc/m²/hour and a urine specific gravity of 1.010 or less. Potassium, calcium, and phosphate should not be initially added to hydration fluids (even if patient levels are normal) so as to avoid hyperkalemia, hyperphosphatemia, and/or calcium phosphate precipitation once therapy-induced cell lysis begins.^{2,39,40} If diuresis is required due to overhydration and volume overload, and there is no evidence of hypovolemia or acute obstructive uropathy, mannitol (0.5 mg/kg) or furosemide (0.5–1.0 mg/kg) may be administered.^{2,40}

Alkalinization Alkalinization of urine (urine pH \geq 7.0) with sodium bicarbonate for hyperuricemia was commonly used with hydration but has become controversial due to the fact that at a higher urinary pH, although urate is more soluble, xanthine and hypoxanthine are less soluble and alkalinization with concomitant allopurinol treatment may result in the formation of xanthine obstructive uropathies.^{2,39} Of note, higher urinary pH also increases the formation of calcium phosphate crystals and can exacerbate hypocalcemia. Based on the potential complications of alkalinization, the use of this form of TLS prevention and/or treatment is no longer recommended.⁴⁰

Allopurinol Allopurinol prevents the formation of uric acid by inhibiting the enzyme xanthine oxidase and can be used effectively as prophylaxis to prevent uric acid nephropathy. However, allopurinol only inhibits the formation of new uric acid and does not remove existing uric acid. In addition, it allows the build up of metabolic products such as hypoxanthine and xanthine, which are even less soluble than uric acid. In cases of renal failure, allopurinol levels should be adjusted to alleviate formation of these products, and the renal excretion of allopurinol itself.⁴¹ In general, only patients without TLS who are at low risk for developing TLS are considered candidates for allopurinol prophylaxis (Figure 2).^{2,5} This has been confirmed by a medical decision model developed by an international panel of experts.⁵

Rasburicase Rasburicase (Elitek, Sanofi-aventis) is the recombinant form of urate oxidase, an enzyme which cannot be produced in humans. Rasburicase catalyzes the conversion of poorly soluble uric acid into allantoin, which is rapidly and easily excreted by the kidneys.^{41–43} Rasburicase is indicated for the initial management of plasma uric acid levels in pediatric patients with leukemia, lymphoma, and solid tumor malignancies, who are receiving anti-cancer therapy expected to result in tumor lysis and subsequent elevation of plasma uric acid.

In contrast to allopurinol, rasburicase can reduce existing plasma uric acid. A randomized trial investigating the efficacy of rasburicase prophylaxis compared with allopurinol in children with lymphoma or leukemia who are at high-risk for TLS, demonstrated a clear benefit with rasburicase. The uric acid area under concentration time curve (AUC)_{0–96} hour was significantly lower in the rasburicase treated patients (128 \pm 70 mg/hour/dL) compared with those treated with allopurinol (329 \pm 129 mg/hour/dL). The results showed an 86% reduction in initial plasma uric acid levels with rasburicase treatment compared with 12% obtained with allopurinol treatment. Patients who were hyperuricemic at baseline had reduction of uric acid levels of more than 8 mg/dL within 4 hours of treatment with rasburicase.⁴⁴ The benefit of prophylactic rasburicase was confirmed in other patients with cancer.^{45–47} In general, response to rasburicase is rapid, and the treatment is well tolerated.^{44,46–48}

In patients at highest risk of developing TLS, rasburicase is generally recommended as the preferred prophylaxis (Figure 2).^{2,5,42,49} It is recommended that these patients receive rasburicase as a 30-minute infusion therapy in an inpatient setting. Rasburicase is contraindicated in patients with the glucose 6-phosphate dehydrogenase (G6PD) deficiency, since it can lead to hemolytic anemia. Prior to rasburicase treatment, patients should be assessed for G6PD deficiency, particularly in populations of African or Mediterranean descent.^{38,50}

Awareness of TLS risk and the use of prophylactic measures should minimize the risk of TLS, and therefore allow CLL patients to stay on treatment and thereby improve their outcome. When TLS does occur, treatment is required as a matter of urgency in order to avoid possible life-threatening consequences and unnecessary delays in the treatment of CLL.

Treatment of TLS in CLL Patients

Interruption of CLL treatment TLS may occur during treatment or, more often, once therapy has been completed. For those patients who develop TLS while on treatment, dosing may have to be interrupted depending on the urgency of the treatment—for example, patients with acute lymphocytic leukemia generally require

continued therapy, whereas CLL patients can often wait. Depending on the clinical situation, CLL treatment may have to be interrupted until the TLS resolves. After the TLS is resolved, patients can resume CLL treatment once sufficient TLS prophylactic measures have been taken. When LTLS occurs, an aggressive approach is needed in all cases.

Hyperuricemia Allopurinol only prevents new uric acid formation and does not reduce uric acid produced prior to allopurinol initiation. Therefore, it is not suitable for the treatment of hyperuricemia in TLS.² So, in patients with TLS already manifest, rasburicase (0.05–0.20 mg/kg for 1–7 days, depending on the individual situation) is the treatment of choice for hyperuricemia (Figure 2).^{2,5,40,42,49}

Hyperphosphatemia To control hyperphosphatemia, phosphate should be removed from intravenous solutions.² Aluminum hydroxide and aluminum carbonate antacids bind phosphate and can be used to reduce introduction of phosphate into the circulation from the gastrointestinal tract.^{2,49} These can be administered orally or nasogastrically (15 mL: 50–150 mg/kg/24 hour).² In general, control of hyperphosphatemia will control hypocalcemia, and asymptomatic patients should not be given calcium infusions.^{2,51}

In severe cases of hyperphosphatemia, where a patient has renal failure, in patients with TLS hemodialysis, continuous venovenous hemofiltration, continuous arteriovenous hemofiltration, and continuous peritoneal dialysis were all shown to be effective.^{52–54} Of these, in general, hemodialysis is the preferred treatment.⁵⁰

Hypocalcemia As mentioned previously, in asymptomatic patients, hypocalcemia in TLS usually resolves with control of concomitant hyperphosphatemia.⁵⁵ However, in symptomatic patients, the use of intravenous calcium gluconate (50–100 mg/kg) is recommended.^{2,55}

Hyperkalemia Hyperkalemia represents a serious complication which may become life threatening due to cardiac arrhythmias. Aggressive hydration with intravenous fluids is recommended in this setting. In patients with elevated serum potassium levels, potassium should be avoided in oral and intravenous administrations. Sodium polystyrene sulfonate at a dose of 1.0 g/kg with 50% sorbitol orally or rectally is recommended in moderate and asymptomatic patients. Calcium gluconate (10%) is recommended in severe and/or symptomatic patients to prevent life-threatening cardiac arrhythmias.^{2,38,49} Cardiac activity should be monitored continuously and electrolyte levels should be evaluated frequently. Other treatments that can be used for severe hyperkalemia in

the absence or presence of electrocardiographic changes include hypertonic glucose (25% dextrose 2 mL/kg) and intravenous insulin (0.1 unit/kg), loop diuretics, and bicarbonate. Dialysis is recommended in severe and/or symptomatic patients.

Conclusions

Although uncommon, TLS may occur as a result of the rapid killing of tumor cells by CLL treatment. TLS can develop rapidly, produce severe metabolic alterations, and may lead to death. With the availability of new and more effective treatments for CLL, it is likely that the frequency of LTLS and potential CTLS may increase. Therefore, close monitoring and prompt recognition of the signs and symptoms of TLS are crucial. Prevention measures should reinforce the importance of adequate hydration and oral antihyperuricemic agents during and after cytotoxic therapy until the risk of TLS has been reduced with a significant decrease in tumor burden. TLS prevention and treatment measures are necessary to avoid unacceptable toxicities and should aid in keeping patients with CLL on treatment and thereby improving their outcome.

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