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REVIEW

Tumor lysis syndrome in childhood malignancies

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Abstract

Background: Tumor lysis syndrome (TLS) is the most common life-threatening oncological emergency encountered by physicians treating children with lymphoproliferative malignancies. Healthcare providers should be aware of the condition in order to prevent occurrence and prompt timely management to avoid severe consequences.

Objective: To provide an update on the current understanding, evaluation, and management of tumor lysis syndrome in childhood malignancies.

Methods: A PubMed search was performed in Clinical Queries using the keywords 'tumor lysis syndrome' and 'malignancies' with Category limited to clinical trials and reviews for ages from birth to 18 years.

Results: There were 22 clinical trials and 37 reviews under the search criteria. TLS is characterized by acute electrolyte and metabolic disturbances resulting from massive and abrupt release of cellular contents into the circulation due to breakdown of tumor cells. If left untreated, it can lead to multiorgan compromise and eventually death. Apart from close monitoring and medical therapies, early recognition of risk factors for development of TLS is also necessary for successful management.

Conclusions: Prophylactic measures to patients at risk of TLS include aggressive fluid management and judicious use of diuretics and hypouricemic agents. Both allopurinol and urate oxidase are effective in reducing serum uric acid. Allopurinol should be used as prophylaxis in low-risk cases while urate oxidase should be used as treatment in intermediate to high-risk cases. There is no evidence on better drug of choice among different urate oxidases. The routine use of diuretics and urine alkalinization are not recommended. Correction of electrolytes and use of renal replacement therapy may also be required during treatment of TLS.

Keywords: hyperkalemia, hyperphosphatemia, hyperuricemia, hypocalcemia, lymphoproliferative malignancies.

Citation

Cheung WL, Hon KL, Fung CM, Leung AKC. Tumor lysis syndrome in childhood malignancies. Drugs in Context 2020; 9: 2019-8-2. DOI: 10.7573/dic.2019-8-2.

Introduction

Tumor lysis syndrome (TLS) is a potentially life-threatening complication of induction chemotherapy for treatment of childhood malignancies, in particular, lymphoproliferative malignancies.[1–4] TLS is characterized by a group of acute electrolyte and metabolic disturbances caused by massive and abrupt release of intracellular contents such as nucleic acids, uric acid, phosphorus, and potassium into the circulation due to breakdown of tumor cells.[3,5] It is most commonly seen in the first few days after the start of cytotoxic therapy especially in hematological malignancies such as acute lymphoblastic leukemia and high-grade lymphomas (particularly, Burkitt's lymphoma).[3,6] TLS in solid malignancies with a high tumor load, high proliferative rates, or high sensitivity to chemotherapy have also been published in several pediatric case reports.[7–9] Spontaneous TLS, which develops in the absence of cytotoxic therapy, had also been described in children with hematological malignancies.[10–12] As a result of breakdown of tumor cells, potentially fatal metabolic derangements such as hyperkalemia, hyperphosphatemia, hypocalcemia, and hyperuricemia may develop. First manifestations of TLS could be subtle and are commonly seen in oncologic patients without TLS, such as nausea, vomiting, diarrhea, muscle cramps, and paresthesia.[9] Edema, arrhythmias, and seizures are often late presentations.[9]

Therefore, keys to prevention and treatment of TLS include a high index of suspicion, early recognition of metabolic and renal complications, and prompt of management of the condition, which includes both prophylaxis and treatment. An awareness of its physiologic consequences, predisposing risk factors, and knowledge on updated management measures are essential prerequisites. This review aims to provide an update on the current understanding, evaluation, and management of TLS in childhood malignancies.

Methods

A PubMed search was performed in Clinical Queries in April 2019 using the keywords 'tumor lysis syndrome' and 'malignancies' with Category limited to clinical trials and reviews for ages from birth to 18 years. There were 22 clinical trials and 37 reviews under the search criteria. A literature review of these articles was performed. This review is based on but not limited to these articles.

Definition

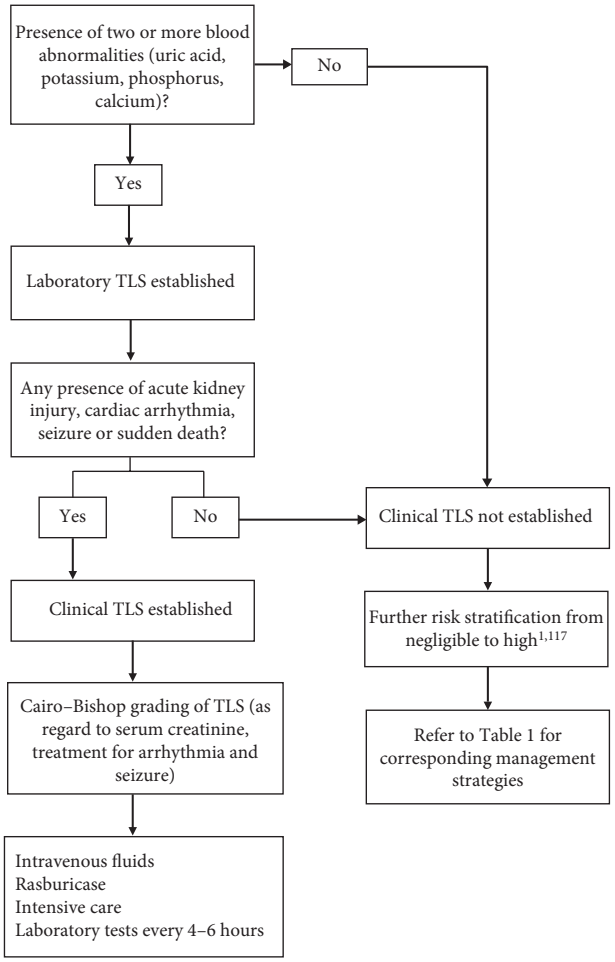
In 1993, Hande–Garrow proposed a system that identified TLS as laboratory or clinical TLS within 4 days of initial chemotherapy.[6] However, this system did not account for patients who had pre-existing abnormal laboratory values before start of treatment and those who had developed abnormal laboratory values after the 4 days of initial therapy.[6]

In 2004, Cairo–Bishop proposed a new classification of TLS (Figure 1).[3,13] According to Cairo–Bishop's definition of TLS, laboratory criteria for its diagnosis require two or more abnormal serum values at presentation, including either a 25% increase or decrease in levels of calcium, uric acid, potassium, or phosphorus within 3 days before or up to 7 days after the start of chemotherapy.[3] The presumption for laboratory diagnosis is that the patient has or will receive adequate hydration (with or without alkalinization) and a hypouricemic agent(s).[14] Criteria for the diagnosis of clinical TLS require the presence of laboratory TLS plus one or more clinical complications, which could be renal insufficiency (defined as serum creatinine more than or equal to 1.5 times the upper limit of normal), cardiac arrhythmias, seizures, or sudden death.[3] These clinical complications should not be directly or probably attributable to a therapeutic agent.

In 2011, Howard and colleagues suggested that two or more abnormal laboratory values should be present simultaneously to define laboratory TLS as abnormality that developed at a later time could be unrelated to TLS. These authors also suggested that a 25% change should not be considered as a criterion, as such a change could be insignificant unless the values are out of the normal range. Lastly, symptomatic hypocalcemia is also recommended to be included in clinical TLS.[1,13,15]

Nonetheless, the original Cairo–Bishop classification has been widely used to establish guidelines for the prevention and management of pediatric and adult TLS.[14,16]

Figure 1. Classification and management algorithm in children with risk of tumor lysis syndrome (TLS) [1,3,13,117]



A grading system for severity of TLS is also proposed by Cairo–Bishop.[14] There are a total of five grades ranging from Grade 0 to Grade 5, which range from absence of TLS to death, respectively (Figure 1).[13]

Epidemiology

The incidence and prevalence of TLS varies among different malignancies and management strategies. Generally, bulky, aggressive, treatment-sensitive tumors, as well as non-implementation of prophylactic measures, are associated with higher frequencies of TLS.[15] Studies have quoted incidence of TLS ranging from 4.4% to 53.6% in hematological malignancies of childhood.[10,15–20]

The majority of these patients have laboratory TLS alone. However, some may progress into clinical TLS.[15,16] In a resource-limited setting, this proportion of patients can reach 15.9%.[16] TLS-related mortality of up to 21.4% was reported in pediatric patients with hematological malignancies.[21–23]

Pathophysiology

TLS is a direct consequence of rapid lysis of malignant cells with the release of intracellular metabolites into the circulation.[1,7,24,25] As the load of circulating intracellular products increases, the homeostatic control mechanisms of such substances are overwhelmed, resulting in the clinical sequelae of TLS. Among the cellular products, potassium, phosphorus, and nucleic acids play a major role in the pathophysiology of TLS. Although TLS can occur spontaneously, it is most often seen 48–72 hours after initiation of chemotherapy.[26,27]

Hyperkalemia

Hyperkalemia is the most rapidly fatal consequence of TLS. It is often the first observed effect of TLS and can occur within 6 hours after the start of chemotherapy.[28,29] Lysis of tumor cells lead to the release of large amounts of potassium, a major intracellular ion, into the circulation.[25,30] Moreover, serum potassium level is also raised by co-existing renal failure and acidosis.[31] Severe hyperkalemia results when uptake capacity by muscle and liver is exceeded.[32,33] Initial manifestations of hyperkalemia include neuromuscular effects, such as muscle weakness and paresthesia, as well as electrocardiogram abnormalities, such as peaked T waves, prolonged PR and QRS interval, and sine wave morphology. Without intervention, devastating complications, for example, cardiac dysrhythmias, ventricular tachycardia, ventricular fibrillation, or cardiac arrest, may ensue.[34]

Hyperphosphatemia

Tumor cells may contain four times more intracellular phosphate as compared to normal mature lymphoid cells.[6] Rapid release of phosphate stores can overload the kidney's excretory capacity, resulting in hyperphosphatemia.[35–37] Symptoms of hyperphosphatemia include nausea, vomiting, diarrhea, lethargy, and seizures. In general, hyperphosphatemia is more commonly associated with TLS that occurs after chemotherapy initiation rather than spontaneous TLS. This is because in spontaneous TLS, tumor cells are able to reuse the released phosphorus for regeneration of new tumor cells, and thus they are less likely to exhibit extreme hyperphosphatemia.[38]

More importantly, phosphates in the blood can bind to calcium cations, leading to hypocalcemia. Severe hypocalcemia can cause arrhythmias, hypotension, tetany, and muscle cramps.[34,39] In addition, calcium phosphate precipitation in renal tubules and cardiac conduction systems can lead to renal failure and cardiac failure, respectively.[35–37] In acute renal failure, decreased calcitriol levels can also cause hypocalcemia. In fact, upon the use of highly effective hypouricemic drugs, calcium phosphate precipitation becomes the major cause of acute kidney injury in TLS.[6,37,40]

Hyperuricemia

Lysed tumor cells release purine nucleic acids, which are metabolized into xanthine. Xanthine is then metabolized into uric acid by hepatic xanthine oxidase, resulting in hyperuricemia. Uric acid is poorly soluble in water, and its solubility is even poorer in an acidic environment. As the concentration of uric acid increases along the kidney tubules, the likelihood of uric acid crystal formation and precipitation increases, causing tubular obstruction and urate nephropathy. With the development of hypouricemia drugs, hyperuricemia is no longer the major consequence of TLS.[41] Xanthine, on the other hand, has lower water solubility than uric acid.[42] High concentration of xanthine, especially in patients treated with allopurinol, predisposes these patients to xanthine nephropathy or urolithiasis.[43–48]

Acute renal failure

TLS is also commonly associated with acute renal failure. The most common cause of acute renal failure in TLS is due to the precipitation of uric acid crystals in renal tubules.[3] Decreased tubular flow rate and renal medullary hemoconcentration also contributes to uric acid crystallization.[49] Other mechanisms include calcium-phosphate crystal deposition, xanthine crystallization, tumor infiltration in the kidneys, tumor-associated obstructive uropathy, drug-associated nephrotoxicity, sepsis, and pre-existing volume depletion and/or renal dysfunction.[3,14] Furthermore, lysis of tumor cells releases cytokines, which can exacerbate acute kidney injury, elicit a systemic inflammatory response syndrome, and eventually cause multiorgan failure.[24,50]

Risk factors

In recent decades, a number of risk-prediction models for TLS have been proposed for children with hematological malignancies.[9,19,51–53] However, each of these models is applicable to certain oncological diseases only. They also lack standardized supportive care guidelines for respective diseases and have complex scoring systems.[1,49] In 2010, an international expert TLS panel developed recommendations for risk stratification of TLS in children and adults with solid and hematological malignancies.[11] This model classified TLS into low, intermediate, and high-risk types. The classification was based on three phases: first, to confirm the presence of laboratory TLS (defined by Hande–Garrow and Cairo–Bishop), then to define risk according to patient and disease characteristics, and lastly to perform risk adjustment by the degree of renal impairment. Associated TLS prophylaxis for each type is also proposed. This has provided a relatively simple clinical tool for health care providers in the management of both pediatric and adult oncology patients. In 2011, Howard and colleagues developed another approach to standardize the definition of TLS and the supportive care

Table 1. Risk stratification and respective management advice of TLS proposed by Howard and colleagues.[1,117]

Risk	Serum potassium, phosphorus, calcium, creatinine, uric acid, urine output	Cancer mass and cell-lysis potential	Management
Negligible	≤1 abnormal value	Small or resected localized tumor OR Medium size tumor with low cell-lysis potential	No prophylaxis or monitoring required
Low	≤1 abnormal value	Medium size tumor with medium/unknown cell-lysis potential* OR Large cancer mass with low cell-lysis potential	Intravenous fluids Allopurinol Daily laboratory tests
Intermediate	≤1 abnormal value	Large cancer mass with medium/unknown cell-lysis potential	Intravenous fluids Allopurinol or rasburicase Laboratory tests every 8–12 hours
High	Can be absent	Medium or large cancer mass with high cell-lysis potential OR Established laboratory TLS	Intravenous fluids Rasburicase Cardiac monitoring Laboratory tests every 6–8 hours
Established	≥2 abnormal values	Established clinical TLS	Intravenous fluids Rasburicase Intensive care Laboratory tests every 4–6 hours

*Patient should not have pre-existing nephropathy, dehydration, acidosis, hypotension, or nephrotoxin exposure. If present, risk should be upgraded to intermediate.
TLS: tumor lysis syndrome.

guidelines for each cancer type.[1,49] In this approach, the risk types for TLS are classified into five categories with respective management recommendations (Table 1). In summary, risk for development of TLS depends on multiple factors, which could be categorized into tumor and patient characteristics and management-related issues (Table 2).[1,14,49,54–56]

Management

Early identification of patients at risk for TLS is essential for timely management. The best management of TLS is prevention. Prophylactic measures should be applied to patients at risk of TLS. Preventive measures include aggressive fluid management, use of diuretics, and hypouricemic agents. Treatment strategies, apart from the use of hypouricemic agents, include correction of electrolytes and use of renal replacement therapy. Close monitoring of renal and cardiac parameters is also important in the management of these patients.

Fluid management

Volume depletion is a major risk factor for TLS. Aggressive hydration and diuresis are fundamental to the prevention and management of TLS. Adequate hydration improves the intravascular volume, enhances renal perfusion and glomerular filtration, and further promotes the excretion of uric acid, potassium, and phosphate. This may also delay and prevent the need for renal replacement therapy.[1,14,29,49,57] Aggressive hydration refers to hyperhydration using intravenous crystalloids of 2.5 (up to 3) L/m^2/day to achieve a target urine output of at least 4 ml/kg/hour for infants and 100 ml/m^2/hour for older patients.[1,49,58] It is also prudent to limit the potassium content in intravenous fluids. Use of loop diuretics is also commonly recommended in clinical practice if urine output is suboptimal after achieving adequate hydration or if the patient is prone to volume overload.[1,32,33,49] Furosemide may be considered for the normovolemic patient with hyperkalemia or for the patient with obvious fluid overload. However, routine use of diuretics is not recommended as use of diuretics may lead to volume depletion and may contribute to calcium phosphate and uric acid precipitation in renal tubules in patients with volume depletion. The use of diuretics is contraindicated in patients with obstructive uropathy.[14,32,33] Current recommendations on diuretic use are based on expert opinions, and there have been no published evidenced-based studies assessing the role of diuretics in the management of TLS yet.

Table 2. Risk factors for development of TLS.[25,26,54–56,117–123]

Category	Risk factors
Tumor characteristics	Tumor type: TLS occurs most frequently in patients with non-Hodgkin's lymphoma and other hematologic malignancies, particularly Burkitt's lymphoma, acute lymphoblastic leukemia, and acute myeloid leukemia. Tumor burden: Larger tumor mass (>10 cm), higher number of cells that will lyse with treatment (≥25,000 circulating tumor cells/μL),[15] tumor infiltration as evidenced by organomegaly (particularly renal infiltration or urine outflow tract obstruction), and bone marrow involvement are signs of high tumor load. Rate of proliferation: The higher the level of lactate dehydrogenase (>2 times the upper limit of normal range), which is a marker for tumor proliferation, the higher the risk for TLS. Sensitivity to anticancer therapy: Malignancies that are more sensitive to chemotherapy have a higher rate of cell lysis and thus pose a greater risk to TLS.
Patient characteristics	Nephropathy before diagnosis of cancer: Pre-existing nephropathy of any cause, such as hypertension and diabetes, predisposes the patient to higher risk of TLS. Pre-existing or co-existing conditions causing impaired kidney perfusion: These include conditions such as dehydration, volume depletion, and hypotension. In such conditions, urine flow in kidney tubules are reduced. Thus, solutes concentration in tubules increases and can cause crystallization, leading to nephropathy. Pre-existing hyperuricemia: Raised baseline serum uric acid (>450 μmol/L) increases the risk of TLS. High pretreatment lactate dehydrogenase: Baseline serum lactate dehydrogenase greater than twice the upper limit of normal increases risk of TLS.
Management related	Inadequate hydration: Hypovolemic state decreases rate of urine flow in kidney tubules and facilitates solutes crystallization and precipitation, causing acute kidney injury. Exogenous potassium: Exogenous sources of potassium such as intravenous fluids, medications, or food may enhance the risk of development of TLS. Exogenous phosphate: Dietary phosphate could be an additional load to high levels of serum phosphate from tumor lysis, causing an extra burden to kidneys' excretion. Exposure to nephrotoxin: Nephrotoxic agents such as vancomycin, aminoglycosides, and contrast agents for imaging increase the risk of acute kidney injury from tumor lysis. Delayed uric acid removal: The longer the uric acid level remains high, the greater the risk of crystal formation and kidney injury. Intensity of initial anticancer therapy: The higher the intensity of initial chemotherapy, the greater the rate of tumor cells lysis and thus a higher risk of TLS. Choice of chemotherapy: Cases of TLS with use of certain chemotherapeutic agents, for example, alvocidib, dinaciclib, obinutuzumab, venetoclax, and rituximab, have been reported.

TLS: tumor lysis syndrome.

Urine alkalinization

Urine alkalinization with the use of intravenous sodium bicarbonate solution was widely advocated for the management of TLS. However, this practice has to be carried out with caution. Theoretically, urine alkalinization increases the solubility of uric acid and promotes its excretion. On the other hand, it decreases the solubility of calcium phosphate and may increase the risk of calcium phosphate precipitation. The resulting alkaline serum pH also promotes albumin-calcium binding and exacerbates hypocalcemia.[7] Moreover, the solubility of xanthine and hypoxanthine is low in alkaline conditions and can cause xanthine crystal precipitation and obstructive nephropathies, especially in cases managed

with allopurinol and rasburicase.[3,14,41] The only indication for alkalinization of urine is in patients with metabolic acidosis.

Xanthine oxidase inhibitors

Allopurinol is a xanthine analog. It acts as a competitive inhibitor of xanthine oxidase, blocks the conversion of purine metabolites into uric acid, and has been shown to prevent the development of obstructive uropathy caused by precipitation of uric acid crystals in renal tubules.[14,59,60] In view of its mechanism of action, allopurinol does not reduce pre-existing serum uric acid level. Therefore, the reduction of serum uric acid level may take several days.[61] Thus, allopurinol is recommended to be used for prophylaxis in low to intermediate risk of TLS rather than treatment of established TLS.[1,14,49,62] For patients with pre-existing hyperuricemia, urate oxidase is the preferred hypouricemia agent.

Allopurinol prophylaxis should be initiated at least 12–24 hours prior to start of chemotherapy and continued until uric acid levels are normalized, and tumor burden and white cells count have returned to low risk levels (≤50,000/μL for acute lymphoblastic lymphoma and ≤10,000/μL for acute myeloid leukemia).[14] Allopurinol is usually given orally. For patients who are unable to tolerate the medication orally, allopurinol can be given intravenously. The oral dosage for children is 300–450 mg/m^2/day in three divided doses up to 400 mg daily. In infants weighing <10 kg, the dose is 3.3 mg/kg every 8 hours.[58,63] The dosage would need to be adjusted in the presence of acute kidney injury, leading to a reduction in creatinine clearance.

Urate oxidase

Urate oxidase is an enzyme that is present in most mammals that converts uric acid to allantoin. Allantoin is five- to ten-fold more soluble in urine than uric acid and is readily excreted.[62] However, this enzyme is absent in humans due to a non-sense mutation in the coding region. Urate oxidase is therefore widely used in patients with cancer for prevention and treatment of hyperuricemia. There are two types of urate oxidase: non-recombinant type Uricozyme® (Sanofi-Aventis, United States) and recombinant type rasburicase. Non-recombinant urate oxidase Uricozyme is a natural uricase obtained from *Aspergillus flavus* cultures, while recombinant urate oxidase rasburicase is obtained by recombinant DNA technique from a genetically modified strain of *Saccharomyces cerevisiae*, which is cloned from a strain of *A. flavis*.[33,64,65]

A recent Cochrane systematic review of (randomized) controlled clinical trials on urate oxidase for prevention and treatment of TLS in children with cancer found that although urate oxidase might be effective in reducing serum uric acid in numerous uncontrolled studies, there is little evidence supporting its effectiveness in preventing or treating TLS.[66] In the Cochrane systematic review, there were only two randomized controlled trials and five controlled clinical trials on the use of urate oxidase in the prophylaxis of TLS, and there were no trials on its use in the treatment of established TLS.[66] Despite the paucity of evidence in significant clinical benefits, the authors of the Cochrane systematic review suggested that this could be a false negative result due to inadequate sample size of the existing clinical trials and that its probable effectiveness in reducing serum uric acid could be an important surrogate outcome.[66] Trials of larger sample size are needed to evaluate the role of urate oxidase for the prevention and treatment of TLS in children.

Uricozyme has been used as a uricolytic agent for the past several decades. It is administered by intravenous infusion at 100 units/kg/day. However, due to product-related impurities, it can be complicated with severe acute hypersensitivity reactions such as anaphylaxis and bronchospams in 5% of patients.[62,67–69]

Rasburicase was then developed in 2001 to reduce the occurrence of these reactions. It is the drug of choice for intermediate- to high-risk TLS patients in view of its quicker onset of action than that of allopurinol.[1,67,70–76] Rasburicase is administered by intravenous infusion at 0.2 mg/kg/dose once daily for up to 5 days.[3,9,58]

The optimal treatment duration has not been determined.[70,71,77–83] Further research includes the optimal number of doses needed, optimal dose based on uric acid levels and tumor burden, dosing in obese patients, and maximum dose.[84] Possible side effects from rasburicase, such as anaphylaxis and methemoglobinemia, are rare (<1%).[19,70,82,83] It is also important to note that urate oxidases can cause hemolytic anemia in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency and is therefore contraindicated. It is recommended that clinicians screen for G6PD deficiency prior to urate oxidase use in patients at risk, specifically in males of African, Southeast Asian, and Mediterranean ethnicity.[9,85,86] However, this is not always feasible, as TLS often progresses quickly if treatment is delayed. In such cases, strict monitoring for signs and symptoms of hemolytic anemia after administration of urate oxidase is crucial.[79,85–87]

Novel xanthine oxidase inhibitors and urate oxidase

Febuxostat is a novel xanthine oxidase inhibitor developed in early 2000s; it lacks the hypersensitivity profile of allopurinol. This is because febuxostat is not a purine analog and therefore had little effects on other enzymes involved in purine and pyrimidine metabolism.[88,89] As it is metabolized in the liver, it does not require dosage adjustments in patients with renal impairment, making it a feasible alternative to allopurinol for patients with allopurinol hypersensitivity or renal impairment.[7,76] A recent phase III study comparing febuxostat and allopurinol

for the prevention of TLS in adults showed a significant lower serum uric acid in the group using febuxostat with comparable renal function preservation and safety profile.[90]

However, in 2019, based on the preliminary results from a safety clinical trial on febuxostat in adults, the US Food and Drug Administration recommended febuxostat to be reserved for use in patients who have failed or do not tolerate allopurinol, as febuxostat showed an increased risk of heart-related deaths and death from all causes.[91] Moreover, there have been no clinical randomized trials on the use of febuxostat in childhood TLS.[7] Large-scale studies are needed to define the optimal febuxostat dosage, explore the most appropriate population for its administration, and better define its safety profile.[92]

Y-700 is another newly synthesized xanthine oxidase inhibitor that showed a more potent and a longer lasting hypouricemic action than allopurinol in hyperuricemic rats.[93] In rat models and in healthy adult male volunteers, Y-700 had high oral bioavailability.[93,94] Unlike allopurinol, it is hardly excreted in kidneys but primarily eliminated by liver and excreted in feces, making it a safe alternative for patients with renal failure.[93,94] However, to the best of our knowledge, there have been no clinical trials on use of Y-700 in TLS yet.

In view of the highly immunogenic potential of traditional urate oxidases, which predisposes patients to risk of anaphylaxis with repeated treatment courses, novel urate oxidases are developed.[83] These urate oxidases are covalently conjugated with polyethylene glycol (PEG) to convert them into less antigenic variants with longer half-lives.[95,96] Examples of such novel agents include pegloticase, which is derived from a mammalian source, and uricase PEG 20, which originates from *Escherichia Coli*. However, they are not approved for treatment of TLS currently. Adult clinical trials are underway, and further studies on their efficacy and safety profile in children with TLS are needed.[95,96]

Correction of electrolytes

Hyperkalemia is the most devastating component of TLS as it can cause sudden death due to cardiac dysrhythmia. Oral or intravenous sources of potassium should be limited or even eliminated in patients at risk of TLS.[14] Standard treatment for asymptomatic hyperkalemia include oral or rectal administration of sodium polystyrene sulfonate.[3]

For symptomatic patients, more aggressive treatment should be used, such as administration of rapid acting insulin and dextrose infusion, which act by increasing intracellular movement of potassium ions from extracellular space.[3] A serum potassium level ≥7 mmol/L represents medical emergency and probably warrants renal dialysis.[14] In case of significant hyperkalemia leading to electrocardiogram changes, cardiac arrhythmias, cardiac dysfunction, and neurological dysfunction such as seizures, slow infusion of calcium gluconate with cardiac monitoring should be considered to block potassium effects on cardiac cell membranes.[1,49] Upon use of intravenous calcium, especially in cases with a calcium–phosphorus product exceeding 70 (serum calcium [mg/dL] × serum phosphorus [mg/dL]), physicians have to watch out for the possibility of formation of calcium–phosphate products, which may lead to acute kidney injury and calcifications of soft tissue.[1,49,97–99]

Like the management of potassium, oral and intravenous intake of phosphorus should be restricted in patients at risk for TLS. Clinicians have to ensure adequate hydration and may use phosphate binders to reduce intestinal absorption of phosphorus present in meals.[100] There are three types of phosphate binders: aluminum-containing (such as aluminum hydroxide), calcium-containing (such as calcium carbonate), and sevelamer.[101–103] Calcium-based phosphate binders should not be used in patients with elevated calcium levels in view of risk of calcium phosphate crystallization and organ injury.[14,34,104] In refractory cases, dialysis should be the management of choice.[3] Intervention is not required in patients with asymptomatic hypocalcemia.[1,14,49] For symptomatic hypocalcemia, for example, with cardiac arrhythmia, seizure, or tetany, patients should be treated with slow intravenous calcium gluconate infusion at lowest dose with cardiac monitoring.[1,14,49] The aim is to relieve symptoms but not to solely treat the numbers as excessive serum calcium increases calcium phosphate product and crystallization.[1,49]

Renal replacement therapy

It was demonstrated that there is ongoing risk of acute kidney injury and associated need for renal replacement therapy in patients with TLS.[105] Indications for renal replacement therapy in TLS are similar to other patients with other causes of acute kidney injury, such as significant fluid overload, uremia, and severe electrolyte, and metabolic disturbances, yet with lower thresholds.[1,49,106] This is particularly true in TLS cases with oliguria because of potentially rapid release and accumulation of electrolytes and metabolites, which could lead to sudden death.[1,14,34,49,104] Hyperphosphatemia-induced symptomatic hypocalcemia may also warrant dialysis, in which continuous renal replacement therapies may be the preferred modality as phosphate clearance with dialytic therapy is time dependent.[1,107–109] For these reasons, continuous renal replacement therapies such as hemofiltration, hemodialysis, and hemodiafiltration are preferred rather than peritoneal dialysis, as these approaches result in better phosphate and uric acid clearance rates and faster clinical improvement.[38,110] There are no major trials showing which approach of hemodialysis is more superior than the other. For most patients, intermittent hemodialysis may be enough. However, in patients with rebound of electrolytes with intermittent hemodialysis, continuous renal replacement therapies may be required.[7,107,111] Dialysis should be carried out until there is adequate return of renal function and urine output. Prophylactic continuous renal

replacement therapy in children at high risk of TLS was shown to be beneficial in a small study.[112] Larger randomized studies will be necessary to provide more evidence for this strategy.

Monitoring

Physicians should stratify patients with malignancies for risk of TLS. As frequent monitoring and assessment is required for patients at high risk of TLS, patients might need to be transferred to centers with intensive care facilities.

Renal function monitoring in terms of urine output is of utmost importance during the management of TLS. Fluid balance should be monitored with urine output as TLS could lead to oliguria by obstructive uropathy with precipitation of calcium-phosphate, xanthine and uric acid products. Moreover, hyperhydration can lead to fluid overload in patients at risk.[32,33] Measurement of electrolytes, creatinine, and uric acid should be done up to every 6–8 hours in patients at high risk for TLS after the start of cytotoxic therapy.[1,49] During the period at risk for TLS, as well as with specific treatment such as intravenous calcium administration, cardiac monitoring is also necessary for detection of arrhythmias. Monitoring should continue over the entire period at risk.[1,49]

Prognosis

Many confounding factors may influence the clinical outcomes of patients with TLS, early identification of patients at risk, early initiation of prophylactic measures, and prompt treatment of complications such as electrolyte imbalances and acute renal failure.[1,49] Severe hyperkalemia may predispose the patient to cardiac arrhythmia, and severe hypocalcemia may predispose the patient to seizures. While pediatric studies on factors predicting outcomes of TLS are lacking, adult studies have been carried out to look for predictors of mortality in TLS. Predictors for hospital mortality include the presence of acute kidney injury and dialysis requirements, cardiac arrhythmias, and sepsis.[113–116] TLS is uncommon in relapsed malignancies as tumor cells are more chemoresistant.[33]

Summary

Clinicians should be aware of the risk factors for TLS in order to prompt timely management. Prophylactic measures to patients at risk of TLS include aggressive fluid management and judicious use of diuretics and hypouricemic agents. Both allopurinol and urate oxidase are effective in reducing serum uric acid. Allopurinol should be used as prophylaxis for low-risk cases while urate oxidase as treatment for intermediate- to high-risk cases. There is no evidence on better drug of choice among different types of urate oxidases. The routine use of diuretics and urine alkalinization are not recommended. Correction of electrolytes and use of renal replacement therapy may also be required during treatment of TLS.

Paucity of pediatric data on prognosis of TLS as well as lack of pediatric evidence on uricosuric agents precludes the development of specific guidelines on TLS of childhood. Further large-scale pediatric studies on predictors of outcome in TLS will be helpful in identifying children at risk of worse prognosis. Large-scale randomized controlled trials on urate oxidases and novel uricosuric agents in children are also particularly helpful to define effectiveness and safety profiles of various drugs and dosage regimes. Our extensive review confirms that there does not seem to be any randomized trials on novel xanthine oxidase inhibitors and urate oxidase or new information regarding TLS treatment for children.

Contributions: All authors contributed equally to the preparation of this review. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Disclosure and potential conflicts of interest: The authors declare that they have no conflicts of interest relevant to this manuscript. The International Committee of Medical Journal Editors (ICMJE) Potential Conflicts of Interests form for the authors is available for download at https://www.drugsincontext.com/wp-content/uploads/2020/01/dic.2019-8-2-COI.pdf

Acknowledgements: None.

Funding declaration: There was no funding associated with the preparation of this article.

Article URL: https://www.drugsincontext.com/tumor-lysis-syndrome-in-childhood-malignancies/

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Provenance: invited; externally peer reviewed.

Submitted: 26 August 2019; **Peer review comments to author:** 30 October 2019; **Revised manuscript received:** 18 December 2019; **Accepted:** 23 January 2020; **Publication date:** 25 February 2020.

Drugs in Context is published by BioExcel Publishing Ltd. Registered office: Plaza Building, Lee High Road, London, England, SE13 5PT.

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