Prevention and treatment of tumor lysis syndrome, and the efficacy and role of rasburicase

Nael Alakel¹

Jan Moritz Middeke¹

Johannes Schetelig^{1,2}

Martin Bornhäuser¹

¹Department of Internal Medicine I, University Hospital Carl Gustav Carus at the Technische Universität Dresden, Dresden, ²German Bone Marrow Donor Center DKMS, Tübingen, Germany

Abstract: Tumor lysis syndrome (TLS) is a potentially life-threatening condition that occurs in oncologic and hematologic patients with large tumor burden, either due to cytotoxic therapy or, less commonly, spontaneously because of massive tumor cell lysis. TLS is clinically characterized by acute renal failure, hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia. While limited options are available for treating TLS, identifying patients at high risk for developing TLS and prevention in high-risk patients remain an important aspect in the treatment of cancer patients. In general, treatment of TLS consists of intensive hydration, stimulation of diuresis, and, more specifically, in the use of allopurinol and rasburicase. Rasburicase, a recombinant urate oxidase, rapidly and effectively reduces hyperuricemia, which subsequently significantly decreases the risk of acute renal failure and other clinical manifestations of TLS. For this review, a comprehensive literature search using the term “tumor lysis syndrome” and/or “rasburicase” was performed considering articles listed in MEDLINE. Incidence, prevention, and therapy of TLS with a special focus on the role of rasburicase are discussed. We evaluated 120 relevant articles including 35 case reports, 32 clinical trials, and 14 meta-analyses.

Keywords: rasburicase, tumor lysis syndrome, hyperuricemia, acute kidney injury

Introduction

Over recent decades, substantial advances in the treatment of cancer led to an improvement in patient outcome. Due to significant knowledge about tumor biology, several novel agents are now available for a more targeted therapy. Further, established treatments were continuously optimized. However, therapy-related complications remain a challenge in cancer therapy despite large improvements in supportive care leading to therapy-related mortality being responsible for a high proportion of deaths in cancer patients.^{1,2}

Tumor lysis syndrome (TLS) is one of the most common cancer therapy complication related to cancer therapy, first described by Bedrna and Polcák³ in 1929. TLS is a life-threatening condition with high morbidity and mortality, caused by an abrupt release of intracellular metabolites after tumor cell lysis. This leads to series of metabolic manifestations, especially hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcaemia. Besides seizures and cardiac arrhythmias, acute kidney injury (AKI) is the hallmark of TLS, which determines the clinical outcome. The pathophysiologic mechanism of AKI in TLS was first described by Crittenden and Ackerman.⁴ They described a formation of uric acid crystals in the renal collecting system in patients with disseminated gastrointestinal carcinoma and AKI.

Incidence

Overall, the reported incidence of TLS varies due to the variability of patient populations analyzed in TLS studies and case reports. Further, the prevalence varies

Correspondence: Nael Alakel
Department of Internal Medicine I,
University Hospital Carl Gustav Carus
at the Technische Universität Dresden,
Fetscherstrasse 74, 01307 Dresden,
Germany
Tel +49 351 458 2321
Fax +49 351 458 5344
Email nael.alakel@uniklinikum-dresden.de

among different malignancies, used anticancer therapies, and prophylactic procedures. Explained by the high rate of cell turnover and sensitivity to cytotoxic therapies, the incidence is higher among hematologic malignancies.⁵ It is necessary to distinguish between asymptomatic TLS defined by laboratory abnormalities and the symptomatic clinical syndrome, occurring less frequently. In one study, laboratory abnormalities were found in 42% of patients, while clinical TLS occurred in only 6%.⁶ In another study investigating children with acute leukemia, asymptomatic TLS occurred in 70% of patients, but clinically significant TLS occurred in only 3% of cases.⁷ Other studies reported incidences of clinical TLS of 3%–27% among hematologic patients.^{8–10}

Recently, increased incidence of TLS in patients with several forms of solid malignancies including pulmonary, gynecologic, gastrointestinal, neurologic cancers, sarcomas, and other malignancies has been reported.^{11–16} One reason for this is the establishment of targeted therapies with high efficacy in solid tumors. Mirrakhimov et al¹⁷ identified metastatic tumors, decreased renal function, elevated lactate dehydrogenase (LDH), and elevated levels of phosphorus, potassium, and uric acid as potential risk factors for TLS in solid tumors. More recently, increasing incidence of TLS has been reported in the era of highly effective novel anticancer agents like ibrutinib^{18,19} and BCL-2 inhibitors²⁰ in diseases like chronic lymphocytic leukemia (CLL), historically considered as being at low risk for developing TLS. Hematol et al²¹ discussed the incidence of TLS in the era of novel therapy in a detailed review.

As mentioned previously, TLS occurs mainly after conventional chemotherapy. However, corticosteroids, radiation, hormonal agents, or antibodies may also cause a significant TLS.^{22–24} Less frequent, spontaneous TLS can develop prior to initiation of anticancer therapy.^{11,13,25,26} Even invasive procedure like biopsies,¹⁶ embolization,^{27,28} and tumor surgery²⁹ could lead to TLS.

Clinical manifestations and classification

Pathophysiological TLS results from a rapid release of intracellular content after tumor cell lysis, which cannot be compensated by cellular buffering and excretory capacity of the renal tubule. This subsequently leads to a variety of biochemical changes causing different clinical manifestations of TLS. Potassium is mainly intracellularly stored, and excessive tumor cell lysis may lead to hyperkalemia. Hyperkalemia is usually the first and most serious abnormality in TLS. It can cause cardiac arrhythmia and sudden death; therefore,

laboratory tests should be repeated. Hyperphosphatemia leads to formation of calcium phosphate complexes that may be precipitated in tissues such as renal tubules. The resulting secondary hypocalcemia may cause hypotension, tetany, and muscular cramps together with hyperkalemia and cardiac arrhythmia.^{5,30}

Nucleic acids are metabolized to hypoxanthine, then xanthine, and finally by xanthine oxidase in the liver to uric acid. Increased uric acid levels in serum can induce urate crystallization and precipitation in renal tubules. This, together with precipitation of calcium phosphate complexes, leads to AKI. In addition, increased serum uric acid levels may induce AKI by crystal-independent mechanisms, such as renal vasoconstriction, decrease in endothelial cell nitric oxide, and stimulation of the renin–angiotensin system.³¹ The most widely used accepted diagnostic criteria and classification were proposed by Cairo and Bishop.³² Briefly, TLS can be divided into asymptomatic laboratory TLS (LTLS), and clinical TLS (CTLS). LTLS is defined by at least two or more abnormalities in the serum concentrations of uric acid, potassium, phosphorus, and calcium within 3 days before or 7 days after the initiation of chemotherapy. CTLS is defined by the presence of LTLS accompanied with clinical manifestations of renal failure, seizures, or cardiac arrhythmias, which are not a result of anticancer therapy. Based on the severity of clinical manifestations, CTLS was stratified using a grading system from 0 to 5, with 0 indicating no signs of CTLS and 5 indicating death due to CTLS.

TLS is a potentially life-threatening complication of anti-neoplastic therapy. Therefore, prevention is a key principle in TLS management during anticancer therapy. Stratifying patients based on the risk of developing TLS is necessary. Cairo et al³³ published in 2010 a recommendation to stratify cancer patients at risk to develop TLS. Patients are stratified into three risk groups depending on patient-related factors (preexisting renal dysfunction and hyperuricemia) and disease-related factors (tumor type, tumor burden [represented by tumor stage, white blood cell counts (WBC), and LDH levels]).

Prevention and treatment

At least twice-daily monitoring of laboratory abnormalities before and during the first 7 days of anticancer therapy is necessary, especially in patients who are at intermediate and high risk for TLS. It could be useful to begin with a prephase of low-intensity therapy in highly chemosensitive cancers with high tumor burden.^{34,35}

Hydration, electrolyte abnormalities, and renal replacement therapy

In patients with intermediate and high risk for TLS, vigorous hydration and assessment of fluid balance to keep urinary output >100 mL/h 24 hours before starting chemotherapy and through the duration of treatment are the key to management. Special attention should be paid to elderly patients or those with heart failure. In case of low urine output after achieving an optimal state of hydration, loop diuretics are recommended. Thiazide diuretics that increase uric acid levels and interact with allopurinol should be avoided. Asymptomatic hypocalcaemia should not be treated to avoid increasing calcium phosphate precipitation in the kidneys. Symptomatic hypocalcemia should be treated with calcium gluconate.⁵

Hyperkalemia may cause serious cardiac arrhythmias; therefore, potassium should be withheld from hydration fluid. Patients with potassium levels ≥ 6 mmol/L should be closely monitored and immediate measures should be taken (infusion of calcium gluconate, therapy with β -adrenergic agonists, and intravenous infusion of insulin and glucose).

Treating hyperphosphatemia is difficult, especially if accompanied by AKI. Oral phosphate binders are less effective, and their oral administration could be difficult in these patients. Significant hyperphosphatemia is treated best with renal replacement therapy.

Renal replacement therapy in TLS should be considered for patients with persistent hyperkalemia despite adequate therapy, severe acidosis, and volume overload unresponsive to diuretic therapy.

Alkalinization of urine

Alkalinization of urine was historically recommended in the management of TLS due to the possibility that it may increase the solubility of uric acid in urine. However, recent increasing evidence suggests that urine alkalinization is associated with increased precipitation of calcium phosphate in the renal tubules, particularly in patients with hyperphosphatemia. Therefore, alkalinization of urine is not recommended in TLS prophylaxis and therapy anymore.³⁶

Antihyperuricemic therapy

Uric acid levels predict the incidence of TLS and AKI,³⁷ and hyperuricemia plays a key role in developing AKI.³¹ Therefore, monitoring and therapy of hyperuricemia are necessary. Besides hydration, the use of uric acid lowering agent is essential in preventing and treating hyperuricemia. Allopurinol (xanthine oxidase inhibitor) and rasburicase

(recombinant urate oxidase) are the most commonly used antihyperuricemic agents.

Allopurinol

Allopurinol is available as oral and intravenous formulations and prevents the conversion of hypoxanthine to xanthine and xanthine to uric acid. The renal clearance of hypoxanthine and xanthine are ten times higher than that of uric acid. Allopurinol has several drug–drug interactions, especially with 6-mercaptoprine, thiazide diuretics, azathioprine, cyclosporine, cyclophosphamide, and amoxicillin. It is necessary to adjust the dose or monitor serum levels of these drugs. The drug should be discontinued in case of skin rash due to the possibility of severe hypersensitivity reactions. Indeed, the dose of allopurinol needs to be adjusted in case of renal insufficiency. Treatment with allopurinol should be started at least 24 hours before initiation of anticancer therapy and should be continued until normalization of uric acid levels and signs of large tumor burden are absent. However, allopurinol cannot reduce the level of preexisting uric acid and causes increases in serum levels of xanthine and hypoxanthine, which may lead to xanthine nephropathy.³⁸ Therefore, therapy with allopurinol should be restricted in patients at low or intermediate risk for TLS. In case of established TLS, additional treatment options should be considered.

Febuxostat

Febuxostat is a selective xanthine oxidase inhibitor developed in 2004 that is able to effectively reduce uric acid levels.^{39,40} Febuxostat has biliary elimination and needs no dose adjustment in patients with renal impairment.⁴¹ Spina et al⁴² performed a randomized, double-blind study comparing febuxostat with allopurinol in hematologic patients at intermediate or high TLS risk: 346 patients were included and received either allopurinol 200–600 mg or febuxostat 120 mg. Compared to allopurinol, febuxostat showed significantly higher reduction in uric acid levels. Interestingly, no difference in TLS incidence between both arms could be observed. Based on this study, the European Medicines Agency (EMA) approved febuxostat for the prevention and treatment of hyperuricemia in patients undergoing chemotherapy. A Japanese group showed noninferiority of lower dose of febuxostat (60 mg/day) compared to allopurinol.⁴³ Thus, febuxostat represents an attractive alternative to allopurinol in patients with renal insufficiency or hypersensitivity to allopurinol.

Rasburicase

In most mammals, but not in humans, uric acid is oxidized to allantoin using the enzyme urate oxidase. In humans, uric

acid is the end product of purine metabolism. Allantoin is ten times more soluble than uric acid and is easily excreted in urine.⁴⁴ Obtained from *Aspergillus flavus*, a nonrecombinant urate oxidase has been available since 1968.

Nonrecombinant urate oxidase was first used in 1975 to prevent and treat hyperuricemia.⁴⁵ In several studies, it achieved rapid and significant reduction of uric acid levels compared to allopurinol.^{46,47} However, its use was limited because of its high immunogenicity and high incidence of anaphylaxis.

Rasburicase is a recombinant, highly purified urate oxidase enzyme approved for the prevention and therapy of hyperuricemia in pediatric and adult patients. In 2001, Pui et al⁴⁸ were able to show a rapid and sharp reduction of uric acid levels in patients with hematologic malignancies. In many clinical trials, a higher and rapid reduction of uric acid level could be reached using rasburicase compared to allopurinol.^{49,50}

In contrast to allopurinol, rasburicase reduces preexisting hyperuricemia quickly and does not lead to xanthine accumulation. Therefore, it is suitable for patients with preexisting hyperuricemia before anticancer therapy, patients at high risk for TLS, or patients with spontaneous TLS.^{51–54}

Rasburicase does not accumulate in plasma even after several days of treatment.^{47,48} However, in a small Japanese pediatric study rasburicase accumulated slightly on day 5.⁵⁵ It is metabolized by peptide hydrolysis, thus not needing dose adjustment in renal or hepatic dysfunction.^{56,57} Rasburicase has a half-life of 17–21 hours and produces rapid (within 4 hours) and pronounced reductions in plasma uric acid concentrations.

Rasburicase has less drug–drug interaction compared to allopurinol.⁵⁶ It is important to note that the drug can continue to work *ex vivo* in room temperature and therefore lead to falsely low uric acid measurements if the blood is not immediately placed and transported in an ice water bath after collection. The analysis must be performed within 4 hours of collection.

Like all recombinant agents, rasburicase is potentially immunogenic and could cause hypersensitivity reactions; however, it is less immunogenic than nonrecombinant urate oxidase. Antibodies against rasburicase could be isolated in 14% of patients after administration,⁴⁸ but the production of these antibodies was not associated with the occurrence of adverse events (AEs) or neutralizing the rasburicase effect.⁵⁸ Goldman et al⁵⁰ could not find antirasburicase antibodies on day 14 after administration. Similar results were found by Kikuchi et al.⁵⁵

Rasburicase is approved by the US Food and Drug Administration (FDA) and EMA for prevention and treatment of hyperuricemia in pediatric and adult patients with solid tumors and hematologic malignancies receiving anticancer therapy. The FDA-approved dosing regimen is 0.15–0.20 mg/kg/day as a single intravenous infusion for 5 days. EMA approved the dosage of 0.20 mg/kg/day given once daily up to 7 days according to uric acid levels and physician choice.

Although the approved dose of rasburicase is 0.15–0.20 mg/kg/day on several days, accumulating evidence shows the feasibility and efficiency of lower doses and/or shorter course of therapy. Vadhan-Raj et al⁵⁹ performed a comparison between a single dose of rasburicase versus daily dosing for 5 days. Adult patients with hematologic malignancies were treated either with a single dose of rasburicase (0.15 mg/kg), which could be repeated on a daily basis or with daily dosing for 5 days. The single dose of rasburicase was as effective as the prolonged therapy for most patients.⁵⁹ Other trials investigated the efficiency of a single dose of rasburicase regardless of patient's weight. Trifilio et al⁶⁰ described the efficiency of 3 mg rasburicase in patients with hematologic malignancies. About 20% needed a second dose of rasburicase. The successful treatment of hyperuricemia was related to baseline uric acid and not to weight-based administration.⁶⁰ In a study by Coutsouvelis et al,⁶¹ a 3 mg fixed dose was effective in patients at high risk for TLS. Similar results could be shown in smaller case series.^{62–67} Recently, Patel et al⁶⁸ have showed the efficiency of a single fixed dose of 4.5 mg rasburicase in a retrospective study.

A meta-analysis⁶⁹ was performed to investigate the effectiveness of a single fixed dose of rasburicase versus the approved dose for 5 days versus allopurinol across ten studies in adult patients at high risk for TLS. This analysis showed noninferiority of a single fixed dose compared to the approved dose over 5 days and was superior to allopurinol. The single fixed dose was effective for both treatment and prophylaxis of hyperuricemia. Other studies compared weight-based dosing, single fixed doses with 3 mg, and single fixed doses.⁷⁰ Weight-based dosing and all single fixed doses were comparable in normalizing plasma uric acid levels. However, the use of single fixed doses of 6 mg was more effective in reaching a sustained uric acid level reduction compared to the 3 mg dose. To our knowledge, no data is available for the therapy of established TLS, but fixed single dose can be tried in the context of prophylaxis.³⁶ Randomized prospective clinical trials are needed to address this

important issue. A summary of selected studies comparing different doses of rasburicase is shown in Table 1.

The role of hyperuricemia in causing AKI is well known. As previously mentioned, hyperuricemia causes AKI through crystallization and precipitation in renal tubules, in addition to crystal-independent mechanisms. Therefore, reduction of uric acid levels should prevent AKI. There is a case report where an AKI due to severe hyperuricemia in a patient with hemolytic uremic syndrome was successfully treated with rasburicase.⁷¹ To our knowledge, no trial assessed systemically the influence of therapy with rasburicase on mortality in adult patients with TLS. Cheuk et al⁷² reviewed seven controlled trials to assess the role of urate oxidase for the prevention or treatment of TLS in pediatric patients. In all trials uric acid levels could be reduced using urate oxidase. However, just three trials could show that a therapy with urate oxidase significantly reduces mortality compared to allopurinol. Eaddy et al⁷³ showed that patients treated with rasburicase have shorter stays in the intensive care unit compared to allopurinol-treated patients. However, there was no significant reduction in total hospital stay.⁷³ Other factors may be responsible for AKI in the setting of TLS, and reduction of uric acid levels alone could not be enough to prevent AKI.^{74,75}

Rasburicase is generally well tolerated. The most reported AEs are headache, nausea, abdominal pain, mucositis, and mild allergic reactions.^{72,76}

The most serious AEs, including hemolytic anemia, methemoglobinemia, and anaphylaxis, were reported in

<1% of patients.^{72,76} The risk of anaphylaxis may increase with repeated administration of rasburicase. Allen et al⁷⁷ investigated the risk of anaphylaxis after multiple treatment courses of rasburicase: 97 patients who did not develop anaphylaxis during the first rasburicase course were analyzed. Six patients experienced severe anaphylaxis following subsequent treatment with rasburicase, with one fatal outcome. Therefore, attention should be paid to the risk of anaphylaxis in case of subsequent administration of rasburicase, and premedication with antihistamines and corticosteroids may be considered.

Several cases of rasburicase-induced methemoglobinemia are reported in the literature.^{78–82} These cases were described especially in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Hydrogen peroxide, which is a product of uric acid, causes oxidative stress to erythrocytes. In case of G6PD deficiency, erythrocytes are not protected against the oxidation stress, leading to methemoglobin formation and hemolysis. Therefore, rasburicase is contraindicated in patients with G6PD deficiency. A decrease of oxygen saturation besides hemolytic anemia should raise suspicion for methemoglobinemia. It is strongly recommended to screen G6PD deficiency in high-risk patients (male patients from tropical Africa, Middle East, and tropical and subtropical Asia) prior to treatment with rasburicase. As this could be difficult, immediate administration of rasburicase may be necessary. Nguyen and Ness⁸³ described two cases of hemolytic anemia following treatment with rasburicase without presence of G6PD deficiency. Unfortunately, no specific

Table 1 Summary of studies compared different doses of rasburicase

Study	Type of study/population	Dose/time	Results/comments
Vadhan-Raj et al ⁵⁹	Prospective study. Adult patients with hematologic malignancies	Single dose of 0.15 mg/kg versus 0.15 mg/kg daily for 5 days	No difference between two doses
Trifilio et al ⁶⁰	Retrospective study. Adult patients with hematologic malignancies	Single dose of 3 mg	3 mg dose was effective
Coutsouvelis et al ⁶¹	Retrospective study. Adult patients with hematologic malignancies	Single dose of 3 mg	3 mg dose was effective. Small size study
Lee et al ⁶⁵	Pediatric patients with hematologic malignancies	Single dose of 4.5 mg	4.5 mg dose was effective. Small size study
Patel et al ⁶⁸	Retrospective study. Adult oncology patients	Single dose of 4.5 mg	4.5 mg dose was effective
McBride et al ⁷⁰	Retrospective study. Adult oncology patients	Single dose of 3, 6, or 7.5 mg compared with weight-based dose	6 mg dose was effective
Campara et al ⁶²	Retrospective study. Adult patients with hematologic malignancies	Single dose of 0.15 mg/kg	0.15 mg/kg dose was effective
Knoebel et al ⁶⁴	Retrospective study. Adult patients with hematologic malignancies	Single dose of 0.05 mg/kg	0.15 mg/kg dose was effective. Small size study
Vines et al ⁶⁷	Retrospective study. Adult patients with hematologic malignancies	Single dose of 4.5 mg	6 mg dose was effective
Reeves et al ⁶⁶	Prospective study. Adult patients with hematologic malignancies and solid tumors	Single dose of 7.5 mg versus single dose 0.15 mg/kg	No difference between two doses. Small size study

therapy of methemoglobinemia in case of G6PD deficiency is known. However, methylene blue may be helpful if G6PD deficiency is ruled out. No data from the use of rasburicase in pregnant women are available; therefore, rasburicase should be used during pregnancy only if strictly necessary. One case report reported the safe and effective use of rasburicase in a pregnant woman in the third trimester giving birth to a healthy child afterward.⁸⁴

Using rasburicase to prevent and treat TLS is expensive, which may be the major limitation to its use. However, the cost of prolonged length of stay (LOS), stays in intensive care unit, treatment of AKI, dialysis, and established TLS should be considered. The cost effectiveness of rasburicase was evaluated in different studies,^{76,85} and the results were controversial. A pan-European multicenter evaluation study showed that rasburicase could be cost-effective in the prevention and treatment of TLS in pediatric and adult patients with acute leukemia and non-Hodgkin lymphoma (NHL).⁸⁶ Annemans et al⁹ showed that rasburicase is cost-effective for prevention of TLS in pediatric patients with acute leukemia and NHL in European countries. Eaddy et al⁷³ compared the cost of rasburicase and allopurinol for treatment of TLS in pediatric patients. In adult patients, adding allopurinol to rasburicase was associated with higher hospitalization costs and LOS compared with rasburicase monotherapy.⁸⁷ Interestingly, rasburicase reduces critical care stays without significant difference in the overall LOS or total cost. Besides its clinical effectiveness, the cost of a single-dose rasburicase is significantly lower than weight-based dosing and could represent an attractive and reasonable alternative to daily administration.^{60,69}

Our recommendations for prevention and treatment of TLS are summarized in Table 2.

Conclusion

TLS is a life-threatening condition that can occur spontaneously, or more commonly follows anticancer therapy. This serious complication may delay or prevent anticancer therapy. In the era of targeted therapy, the incidence and clinical significance of this complication is increasing. Established TLS is associated with high morbidity and mortality even under adequate therapy. Therefore, the most effective therapy is prevention. Recognition of patients at risk for TLS is pivotal. The most widely accepted diagnostic criteria and classification proposed by Cairo and Bishop³² enable early risk stratification of patients. Allopurinol and rasburicase are known to reduce uric acid levels. Allopurinol has no effect on existing hyperuricemia; thus, it can be preferentially used in patients with low or intermediate risk for TLS. Rasburicase, on the other hand, rapidly reduces existing hyperuricemia. The role of rasburicase in the treatment of established TLS is widely accepted; however, its role in TLS prophylaxis is still controversial. There is clear evidence of its superior efficacy over allopurinol's in reduction of uric acid levels. Nevertheless, limited evidence from randomized controlled trials exists with regard to a reduction of TLS mortality or incidence of AKI with the use of rasburicase. The role of hyperuricemia in developing AKI is well known. Hyperuricemia causes AKI through crystallization and precipitation in renal tubules, in addition to crystal-independent mechanisms. Therefore, reduction of uric acid levels ought to prevent AKI. However, other factors may be responsible for AKI in the

Table 2 Recommendations for prevention and treatment of tumor lysis syndrome

	Low-risk disease	Intermediate-risk disease	High-risk disease
Diagnostic measures	<ul style="list-style-type: none"> No specific measures 	<ul style="list-style-type: none"> Daily monitoring of laboratory abnormalities before and during the first 7 days of anticancer therapy 	<ul style="list-style-type: none"> At least twice daily monitoring of laboratory abnormalities before and during the first 7 days of anticancer therapy
Preventive measures	<ul style="list-style-type: none"> Moderate hydration is recommended 	<ul style="list-style-type: none"> Vigorous hydration Keep urinary output > 100 mL/h Treatment with allopurinol or febuxostat should be started at least 24 hours before initiation of anticancer therapy and should be continued till normalization of uric acid levels and signs of large tumor burden are absent 	<ul style="list-style-type: none"> Vigorous hydration Keep urinary output > 100 mL/h Single dose 6 mg of rasburicase. Repeat doses as necessary. In case of contraindication treatment with febuxostat
Treatment of established tumor lysis syndrome	<ul style="list-style-type: none"> Admission to intensive care unit with continuous cardiac monitoring and monitoring of laboratory abnormalities every 4–6 hours Early nephrology consultation to estimate the indications for renal replacement therapy Correction of electrolyte abnormalities Vigorous hydration, keep urinary output > 100 mL/h Single dose 6 mg of rasburicase. Repeat doses as necessary. In case of contraindication, treatment with febuxostat 		

setting of TLS, and reduction of uric acid levels alone may not be enough to prevent AKI.^{74,75} With regard to economic aspects, some authors described its cost efficiency in terms of LOS, intensive care therapy, and dialysis. Increasing evidence suggests the efficiency of a fixed single dose of rasburicase. In conclusion, patients at low or intermediate risk for TLS can be managed with prophylactic allopurinol, but patients at high risk for developing TLS or with established TLS should receive rasburicase.

Disclosure

The authors report no conflicts of interest in this work.

References

- Ward E, Desantis C, Robbins A, Kohler B, Jemal A. Childhood and adolescent cancer statistics, 2014. *CA Cancer J Clin*. 2014;64(2):83–103.
- Christensen MS, Heyman M, Möttönen M, et al. Treatment-related death in childhood acute lymphoblastic leukaemia in the Nordic countries: 1992–2001. *Br J Haematol*. 2005;131(1):50–58.
- Bedrna J, Polcák J. Akuter harnleiterverschluss nach bestrahlung chronischer leukämien mit röntgenstrahlen. *Med Klin*. 1929;25:1700–1701.
- Crittenden DR, Ackerman GL. Hyperuricemic acute renal failure in disseminated carcinoma. *Arch Intern Med*. 1977;137(1):97–99.
- Coiffier B, Altman A, Pui C-H, Younes A, Cairo MS. Guidelines for the management of pediatric and adult tumor lysis syndrome: an evidence-based review. *J Clin Oncol*. 2008;26(16):2767–2778.
- Hande KR, Garrow GC. Acute tumor lysis syndrome in patients with high-grade non-Hodgkin's lymphoma. *Am J Med*. 1993;94(2):133–139.
- Kedar A, Grow W, Neiberger RE. Clinical versus laboratory tumor lysis syndrome in children with acute leukemia. *Pediatr Hematol Oncol*. 1995;12(2):129–134.
- Montesinos P, Lorenzo I, Martín G, et al. Tumor lysis syndrome in patients with acute myeloid leukemia: identification of risk factors and development of a predictive model. *Haematologica*. 2008;93(1):67–74.
- Annemans L, Moeremans K, Lamotte M, et al. Incidence, medical resource utilisation and costs of hyperuricemia and tumour lysis syndrome in patients with acute leukaemia and non-Hodgkin's lymphoma in four European countries. *Leuk Lymphoma*. 2003;44(1):77–83.
- Arseneau JC, Canellos GP, Banks PM, Berard CW, Gralnick HR, DeVita VT Jr. American Burkitt's lymphoma: a clinicopathologic study of 30 cases. I. Clinical factors relating to prolonged survival. *Am J Med*. 1975;58(3):314–321.
- Okamoto K, Kinoshita T, Shimizu M, et al. A case of spontaneous tumor lysis syndrome in a patient with ovarian cancer. *Case Rep Obstet Gynecol*. 2015;2015:461870.
- Brinton T, Yousuf T, Steinecker G, Rydel J. A case of tumor lysis syndrome in a patient with pancreatic adenocarcinoma treated with low-dose gemcitabine. *Ochsner J*. 2015;15(4):455–456.
- Saleh RR, Rodrigues J, Lee TC. A tumour lysis syndrome in a chemotherapy naive patient with metastatic pancreatic adenocarcinoma. *BMJ Case Rep*. 2015;2015.
- Lobe TE, Karkera MS, Custer MD, Shenefelt RE, Douglass EC. Fatal refractory hyperkalemia due to tumor lysis during primary resection for hepatoblastoma. *J Pediatr Surg*. 1990;25(2):249–250.
- Kushner BH, LaQuaglia MP, Modak S, Cheung N-KV. Tumor lysis syndrome, neuroblastoma, and correlation between serum lactate dehydrogenase levels and MYCN-amplification. *Med Pediatr Oncol*. 2003;41(1):80–82.
- Ascani S, Went P, Liberati AM, Piccaluga PP, Zinzani PL, Pileri SA. Difficult diagnostic and therapeutic cases: Case 1. True thymic hyperplasia in a patient treated for T-cell lymphoma. *J Clin Oncol*. 2004;22(5):953–954.
- Mirakhimov AE, Ali AM, Khan M, Barbaryan A. Tumor lysis syndrome in solid tumors: an up to date review of the literature. *Rare Tumors*. 2014;6(2):5389.
- Kaur V, Swami A. Ibrutinib-associated tumor lysis syndrome in a patient with mantle cell lymphoma: a case report. *J Oncol Pharm Pract*. Epub March 11, 2016.
- Kaur V, Mehta P, Johnsurd J, Govindarajan R. Ibrutinib-associated tumor lysis syndrome in a patient with chronic lymphocytic leukemia. *Blood*. 2014;124(23):3503–3505.
- Tam CS, Seymour JF, Roberts AW. Progress in BCL2 inhibition for patients with chronic lymphocytic leukemia. *Semin Oncol*. 2016;43(2):274–279.
- Howard SC, Trifilio S, Gregory TK, Baxter N, McBride A. Tumor lysis syndrome in the era of novel and targeted agents in patients with hematologic malignancies: a systematic review. *Ann Hematol*. 2016;95:563–573.
- Alkan A, Kütük T, Karcı E, Yaşar A, Hiçsönmez A, Utkan G. Radiation induced tumor lysis syndrome in chronic lymphocytic leukemia. *Turk J Haematol*. 2016;33(3):248–250.
- Chen S-W, Hwang W-S, Tsao C-J, Liu H-S, Huang G-C. Hydroxyurea and splenic irradiation-induced tumour lysis syndrome: a case report and review of the literature. *J Clin Pharm Ther*. 2005;30(6):623–625.
- Abou Mourad Y, Taher A, Shamseddine A. Acute tumor lysis syndrome in large B-cell non-Hodgkin lymphoma induced by steroids and anti-CD 20. *Hematol J*. 2003;4(3):222–224.
- Yun S, Vincelette ND, Phan T, Anwer F. Spontaneous tumour lysis syndrome associated with contrast dye iohexol use in mantle cell lymphoma. *BMJ Case Rep*. 2014;2014.
- Weeks AC, Kimple ME. Spontaneous tumor lysis syndrome: a case report and critical evaluation of current diagnostic criteria and optimal treatment regimens. *J Investig Med High Impact Case Rep*. 2015;3(3):2324709615603199.
- Salsamendi JT, Doshi MH, Gortes FJ, Levi JU, Narayanan G. Acute tumor lysis syndrome after proximal splenic artery embolization. *Radiol Case Rep*. 2016;11(2):90–92.
- Liu PH, Hsu JW, Kung WC, Wu YC, Chang WY, Su CM. Tumor lysis syndrome occurring after transarterial embolization in a 70-year-old man with a hepatocellular carcinoma ruptured in a motor vehicle accident. *Int J Gerontol*. 2014;8(2):100–102.
- Dhar M, Prakash S, Pandey V, Pai VK. Intraoperative tumor lysis syndrome in a child with Wilms' tumor. *Anesth Essays Res*. 2016;10(1):145–147.
- Davidson MB, Thakkar S, Hix JK, Bhandarkar ND, Wong A, Schreiber MJ. Pathophysiology, clinical consequences, and treatment of tumor lysis syndrome. *Am J Med*. 2004;116(8):546–554.
- Abu-Alfa AK, Younes A. Tumor lysis syndrome and acute kidney injury: evaluation, prevention, and management. *Am J Kidney Dis*. 2010;55(5 Suppl 3):S1–S13.
- Cairo MS, Bishop M. Tumour lysis syndrome: new therapeutic strategies and classification. *Br J Haematol*. 2004;127(1):3–11.
- Cairo MS, Coiffier B, Reiter A, Younes A. Recommendations for the evaluation of risk and prophylaxis of tumour lysis syndrome (TLS) in adults and children with malignant diseases: an expert TLS panel consensus. *Br J Haematol*. 2010;149(4):578–586.
- Howard SC, Jones DP, Pui CH. The tumor lysis syndrome. *N Engl J Med*. 2011;364(19):1844–1854.
- Pfreundschuh M. How I treat elderly patients with diffuse large B-cell lymphoma. *Blood*. 2010;116(24):5103–5110.
- Jones GL, Will A, Jackson GH, Webb NJA, Rule S; British Committee for Standards in Haematology. Guidelines for the management of tumour lysis syndrome in adults and children with haematological malignancies on behalf of the British Committee for Standards in Haematology. *Br J Haematol*. 2015;169(5):661–671.
- Ejaz AA, Pourafshar N, Mohandas R, Smallwood BA, Johnson RJ, Hsu JW. Uric acid and the prediction models of tumor lysis syndrome in AML. *PLoS One*. 2015;10(3):e0119497.
- Sood AR, Burry LD, Cheng DKF. Clarifying the role of rasburicase in tumor lysis syndrome. *Pharmacotherapy*. 2007;27(1):111–121.

39. Schumacher HR, Becker MA, Lloyd E, MacDonald PA, Lademacher C. Febuxostat in the treatment of gout: 5-yr findings of the FOCUS efficacy and safety study. *Rheumatology (Oxford)*. 2009;48(2):188–194.
40. Burns CM, Wortmann RL. New drug class gout therapeutics: new drugs for an old disease. *Lancet*. 2011;377(377):165–177.
41. Mayer MD, Khosravan R, Vernillet L, Wu J-T, Joseph-Ridge N, Mulford DJ. Pharmacokinetics and pharmacodynamics of febuxostat, a new non-purine selective inhibitor of xanthine oxidase in subjects with renal impairment. *Am J Ther*. 2005;12(1):22–34.
42. Spina M, Nagy Z, Ribera JM, et al. FLORENCE: a randomized, double-blind, phase III pivotal study of febuxostat versus allopurinol for the prevention of tumor lysis syndrome (TLS) in patients with hematologic malignancies at intermediate to high TLS risk. *Ann Oncol*. 2015;26(10):2155–2161.
43. Tamura K, Kawai Y, Kiguchi T, et al. Efficacy and safety of febuxostat for prevention of tumor lysis syndrome in patients with malignant tumors receiving chemotherapy a phase III, randomized, multi-center trial comparing febuxostat and allopurinol. *Int J Clin Oncol*. 2016;21(5):996–1003.
44. Hochberg J, Cairo MS. Tumor lysis syndrome: current perspective. *Haematologica*. 2008;93(1):9–13.
45. Patte C, Sakiroglu O, Sommelet D. European experience in the treatment of hyperuricemia. *Semin Hematol*. 2001;38(4 Suppl 10):9–12.
46. Patte C, Philip T, Rodary C, et al. High survival rate in advanced-stage B-cell lymphomas and leukemias without CNS involvement with a short intensive polychemotherapy: results from the French Pediatric Oncology Society of a randomized trial of 216 children. *J Clin Oncol*. 1991;9(1):123–132.
47. Pui CH, Relling MV, Lascombes F, et al. Urate oxidase in prevention and treatment of hyperuricemia associated with lymphoid malignancies. *Leukemia*. 1997;11(11):1813–1816.
48. Pui CH, Mahmoud HH, Wiley JM, et al. Recombinant urate oxidase for the prophylaxis or treatment of hyperuricemia in patients with leukemia or lymphoma. *J Clin Oncol*. 2001;19(3):697–704.
49. Cortes J, Moore JO, Maziart RT, et al. Control of plasma uric acid in adults at risk for tumor lysis syndrome: efficacy and safety of rasburicase alone and rasburicase followed by allopurinol compared with allopurinol alone – results of a multicenter phase III study. *J Clin Oncol*. 2010;28(27):4207–4213.
50. Goldman SC, Holcenberg JS, Finklestein JZ, et al. A randomized comparison between rasburicase and allopurinol in children with lymphoma or leukemia at high risk for tumor lysis. *Blood*. 2012;97(10):2998–3003.
51. Coiffier B, Mounier N, Bologna S, et al. Efficacy and safety of rasburicase (recombinant urate oxidase) for the prevention and treatment of hyperuricemia during induction chemotherapy of aggressive non-Hodgkin's lymphoma: results of the GRAAL1 (Groupe d'Etude des Lymphomes de l'Adulte Trial on Rasburicase Activity in Adult Lymphoma) study. *J Clin Oncol*. 2003;21(23):4402–4406.
52. Jeha S, Kantarjian H, Irwin D, et al. Efficacy and safety of rasburicase, a recombinant urate oxidase (Elitek), in the management of malignancy-associated hyperuricemia in pediatric and adult patients: final results of a multicenter compassionate use trial. *Leukemia*. 2005;19:34–38.
53. Rényi I, Bárdi E, Udvardi E, et al. Prevention and treatment of hyperuricemia with rasburicase in children with leukemia and non-Hodgkin's lymphoma. *Pathol Oncol Res*. 2007;13(1):57–62.
54. Shin HY, Kang HJ, Park ES, et al. Recombinant urate oxidase (Rasburicase) for the treatment of hyperuricemia in pediatric patients with hematologic malignancies: results of a compassionate prospective multicenter study in Korea. *Pediatr Blood Cancer*. 2006;46(4):439–445.
55. Kikuchi A, Kigasawa H, Tsurusawa M, et al. A study of rasburicase for the management of hyperuricemia in pediatric patients with newly diagnosed hematologic malignancies at high risk for tumor lysis syndrome. *Int J Hematol*. 2009;90(4):492–500.
56. Pea F. Pharmacology of drugs for hyperuricemia. Mechanisms, kinetics and interactions. *Contrib Nephrol*. 2005;147:35–46.
57. Ueng S. Rasburicase (Elitek): a novel agent for tumor lysis syndrome. *Proc (Bayl Univ Med Cent)*. 2005;18(3):275–279.
58. Pui CH. Rasburicase: a potent uricolytic agent. *Expert Opin Pharmacother*. 2002;3(4):433–442.
59. Vadhan-Raj S, Fayad LE, Fanale MA, et al. A randomized trial of a single-dose rasburicase versus five-daily doses in patients at risk for tumor lysis syndrome. *Ann Oncol*. 2012;23(6):1640–1645.
60. Trifilio SM, Pi J, Zook J, et al. Effectiveness of a single 3-mg rasburicase dose for the management of hyperuricemia in patients with hematologic malignancies. *Bone Marrow Transplant*. 2011;46(6):800–805.
61. Coutsouvelis J, Wiseman M, Hui L, et al. Effectiveness of a single fixed dose of rasburicase 3mg in the management of tumour lysis syndrome. *Br J Clin Pharmacol*. 2013;75(2):550–553.
62. Campara M, Shord SS, Haaf CM. Single-dose rasburicase for tumour lysis syndrome in adults: weight-based approach. *J Clin Pharm Ther*. 2009;34(2):207–213.
63. Hummel M, Buchheidt D, Reiter S, Bergmann J, Hofheinz R, Hehlmann R. Successful treatment of hyperuricemia with low doses of recombinant urate oxidase in four patients with hematologic malignancy and tumor lysis syndrome. *Leukemia*. 2003;17(12):2542–2544.
64. Knoebel RW, Lo M, Crank CW. Evaluation of a low, weight-based dose of rasburicase in adult patients for the treatment or prophylaxis of tumor lysis syndrome. *J Oncol Pharm Pract*. 2011;17(3):147–154.
65. Lee AC, Li CH, So KT, Chan R. Treatment of impending tumor lysis with single-dose rasburicase. *Ann Pharmacother*. 2003;37(11):1614–1617.
66. Reeves DJ, Bestul DJ. Evaluation of a single fixed dose of rasburicase 7.5 mg for the treatment of hyperuricemia in adults with cancer. *Pharmacotherapy*. 2008;28(6):685–690.
67. Vines AN, Shanholtz CB, Thompson JL. Fixed-dose rasburicase 6 mg for hyperuricemia and tumor lysis syndrome in high-risk cancer patients. *Ann Pharmacother*. 2010;44(10):1529–1537.
68. Patel KS, Lau JE, Zembillas AS, Gallagher EM. Single 4.5 mg fixed-dose of rasburicase for hyperuricemia associated with tumor lysis syndrome. *J Oncol Pharm Pract*. Epub April 15, 2016.
69. Feng X, Dong K, Pham D, Pence S, Inciardi J, Bhutada NS. Efficacy and cost of single-dose rasburicase in prevention and treatment of adult tumour lysis syndrome: a meta-analysis. *J Clin Pharm Ther*. 2013;38(4):301–308.
70. McBride A, Lathon SC, Boehmer L, Augustin KM, Butler SK, Westervelt P. Comparative evaluation of single fixed dosing and weight-based dosing of rasburicase for tumor lysis syndrome. *Pharmacotherapy*. 2013;33(3):295–303.
71. Acosta AA, Hogg RJ. Rasburicase for hyperuricemia in hemolytic uremic syndrome. *Pediatr Nephrol*. 2012;27(2):325–329.
72. Cheuk DK, Chiang AK, Chan GC, Ha SY. Urate oxidase for the prevention and treatment of tumour lysis syndrome in children with cancer. *Cochrane Database Syst Rev*. 2014;8(8):CD006945.
73. Eaddy M, Seal B, Tangirala M, Davies EH, O'Day K. Economic comparison of rasburicase and allopurinol for treatment of tumor lysis syndrome in pediatric patients. *Am J Health Syst Pharm*. 2010;67(24):2110–2114.
74. Darmon M, Vincent F, Camous L, et al. Tumour lysis syndrome and acute kidney injury in high-risk haematology patients in the rasburicase era. A prospective multicentre study from the Groupe de Recherche en Réanimation Respiratoire et Onco-Hématologique. *Br J Haematol*. 2013;162(4):489–497.
75. Galaray PJ, Hochberg J, Perkins SL, Harrison L, Goldman S, Cairo MS. Rasburicase in the prevention of laboratory/clinical tumour lysis syndrome in children with advanced mature B-NHL: a children's oncology group report. *Br J Haematol*. 2013;163(3):365–372.
76. Hochberg J, Cairo MS. Rasburicase: future directions in tumor lysis management. *Expert Opin Biol Ther*. 2008;8(10):1595–1604.
77. Allen KC, Champlain AH, Cotliar JA, et al. Risk of anaphylaxis with repeated courses of rasburicase: a research on adverse drug events and reports (RADAR) project. *Drug Saf*. 2015;38(2):183–187.

78. Montgomery KW, Booth GS. A perfect storm: tumor lysis syndrome with rasburicase-induced methemoglobinemia in a G6PD deficient adult. *J Clin Apher*. Epub April 27, 2016.
79. Ng JS, Edwards EM, Egelund TA. Methemoglobinemia induced by rasburicase in a pediatric patient: a case report and literature review. *J Oncol Pharm Pract*. 2012;18(4):425–431.
80. Bucklin MH, Groth CM. Mortality following rasburicase-induced methemoglobinemia. *Ann Pharmacother*. 2013;47(10):1353–1358.
81. Alessa MA, Craig AK, Cunningham JM. Rasburicase-induced methemoglobinemia in a patient with aggressive non-Hodgkin's lymphoma. *Am J Case Rep*. 2015;16:590–593.
82. Roberts DA, Freed JA. Rasburicase-induced methemoglobinemia in two African-American female patients: an under-recognized and continued problem. *Eur J Haematol*. 2015;94(1):83–85.
83. Nguyen AP, Ness GL. Hemolytic anemia following rasburicase administration: a review of published reports. *J Pediatr Pharmacol Ther*. 2014;19(4):310–316.
84. Middeke JM, Bruck N, Parmentier S, Bornhauser M, Schetelig J. Use of rasburicase in a pregnant woman with acute lymphoblastic leukaemia and imminent tumour lysis syndrome. *Ann Hematol*. 2014;93(3):531–532.
85. Oldfield V, Perry CM. Spotlight on rasburicase in anticancer therapy-induced hyperuricemia. *BioDrugs*. 2006;20(3):197–199.
86. Annemans L, Moeremans K, Lamotte M, et al. Pan-European multi-centre economic evaluation of recombinant urate oxidase (rasburicase) in prevention and treatment of hyperuricaemia and tumour lysis syndrome in haematological cancer patients. *Support Care Cancer*. 2003;11(4):249–257.
87. Eaddy M, Seal B, Tangirala K, Davies EH, O'Day K. Economic implications of rasburicase treatment in adult patients with tumour lysis syndrome. *Appl Health Econ Health Policy*. 2012;10(6):431–440.

OncoTargets and Therapy

Publish your work in this journal

OncoTargets and Therapy is an international, peer-reviewed, open access journal focusing on the pathological basis of all cancers, potential targets for therapy and treatment protocols employed to improve the management of cancer patients. The journal also focuses on the impact of management programs and new therapeutic agents and protocols on

Submit your manuscript here: <http://www.dovepress.com/oncotargets-and-therapy-journal>

patient perspectives such as quality of life, adherence and satisfaction. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.

Dovepress