Leukemia & Lymphoma, October 2014; 55(10): 2362–2367

ISSN: 1042-8194 print / 1029-2403 online
DOI: 10.3109/10428194.2013.874010

informa
healthcare

ORIGINAL ARTICLE: CLINICAL

Plasma uric acid response to rasburicase: early marker for acute kidney injury in tumor lysis syndrome?

Emmanuel Canet[1], Morgane Cheminant[1], Lara Zafrani[1], Catherine Thieblemont[2], Lionel Galicier[2], Etienne Lengline[2], David Schnell[1], Danielle Reuter[1], Michael Darmon[3], Benoit Schlemmer[1,4] & Elie Azoulay[1,4]

[1]*Medical Intensive Care Unit and* [2]*Hematology Department, Saint-Louis University Hospital, Paris, France,* [3]*Medical Intensive Care Unit, Saint-Etienne University Hospital, Saint-Etienne, France and* [4]*School of Medicine, Université Paris-Diderot, Sorbonne Paris-Cité, Paris, France*

Abstract

Acute kidney injury (AKI) is associated with high morbidity and mortality in tumor lysis syndrome (TLS). The goal of this study was to assess a practical approach involving a simple risk-prediction model for AKI in patients at high risk for clinical TLS treated according to standardized guidelines. We collected data on 62 patients at high risk for clinical TLS. We evaluated whether the magnitude of the plasma uric acid decrease in response to rasburicase predicted AKI. According to RIFLE criteria (Risk, Injury, Failure, sustained Loss, End-stage kidney disease), 41 (66.1%) patients had AKI. AKI was associated with higher hospital (26.8% vs. 0%, $p = 0.01$) and 6-month (41.4% vs. 9.5%, $p = 0.04$) mortality. The plasma uric acid decrease after rasburicase was significantly larger in patients who did not develop AKI than in those who did (95% vs. 84%; $p < 0.01$). By multivariate analysis, independent determinants of AKI were hypertension and a plasma uric acid decrease smaller than 92.9% 6 h after rasburicase.

Keywords: Tumor lysis syndrome, rasburicase, acute kidney injury

Introduction

Tumor lysis syndrome (TLS) is a life-threatening metabolic complication of hematological malignancies that may occur spontaneously or in response to cytotoxic therapy. In TLS, tumor cells release massive amounts of intracellular components, inducing hyperkalemia, hyperphosphatemia, hypocalcemia, hyperuricemia and acute kidney injury (AKI) [1]. AKI is a dreaded complication of TLS that often requires intensive care unit (ICU) admission and renal replacement therapy (RRT) and is associated with higher hospital and long-term mortality rates [2–5].

Uric acid plays a crucial role in the development of TLS-induced AKI [6]. During TLS, massive release of nucleic acids from tumor cells into the bloodstream results in hyperuricemia [7]. Uric acid can crystallize with phosphate in the distal renal tubules, causing obstructive nephropathy [8]. In addition, emerging experimental and clinical data suggest crystal-independent mechanisms of renal injury. Soluble uric acid may also contribute to AKI by inducing renal vasoconstriction and antiangiogenic, proinflammatory and pro-oxidative effects that impair glomerular perfusion [9].

The prevention of TLS-induced AKI relies on withdrawal of nephrotoxic drugs, intravenous hydration with saline, and the administration of hypouricemic agents prior to and during cancer chemotherapy [1,10,11]. The enzyme urate oxidase converts uric acid to allantoin, which is about five times more soluble than uric acid and is readily excreted in urine [12]. Rasburicase, a recombinant form of urate oxidase, is widely used in patients at high risk for clinical TLS [13–15].

Although consensus guidelines for TLS management have been issued, no reliable marker is available for assessing the risk of AKI in individual patients. Such a marker would help to identify patients requiring early ICU admission and to select the best treatment strategy.

The goal of this study was to assess the hypothesis that the plasma uric acid response to a single rasburicase dose would predict AKI in patients at high risk for clinical TLS. To evaluate this hypothesis, we conducted a hospital-based prospective observational cohort study. We also determined the incidence, clinical features and mortality associated with clinical TLS in our study population.

Materials and methods

As required by our institutional review board (CECIC Clermont Ferrand, IRB no. 5891; Ref: 2007-16), informed consent was obtained from each patient prior to participation in this non-interventional study with anonymous data collection.

Correspondence: Emmanuel Canet, MD, AP-HP, Saint-Louis University Hospital, Medical Intensive Care Unit, 1 avenue Claude Vellefaux, 75010 Paris, France. Tel: + 33-142-499-419. Fax: + 33-142-499-426. E-mail: emmanuel.canet@sls.aphp.fr

Received 1 August 2013; revised 23 November 2013; accepted 7 December 2013

Study design

We included consecutive adults admitted to the Saint-Louis University Hospital, Paris, France, between 1 November 2007 and 31 October 2010, with high-grade hematological malignancies considered at high risk for clinical TLS before chemotherapy initiation. The definition of clinical TLS and criteria used to assess the risk of clinical TLS have been published elsewhere (available in the Electronic Supplemental Material) [1].

Patients were admitted either to hematology wards or, if renal replacement therapy (RRT) was required, to the ICU. The Saint-Louis University Hospital is a 650-bed public hospital with 330 beds for patients with hematological malignancies and solid cancers. The ICU is a closed 12-bed medical unit that admits 750–850 patients per year, of whom about one-third have hematological malignancies. Information on the organization of our ICU and criteria for ICU admission have been published elsewhere [16]. ICU admission policies remained unchanged throughout the study period. At our institution, senior hematologists and intensivists are available 24 h a day, 7 days a week, and work together to manage all high-risk hematology patients.

AKI was diagnosed based on RIFLE criteria (Risk, Injury, Failure, sustained Loss, End-stage kidney disease) [17]. The estimated glomerular filtration rate (eGFR) was determined in each patient using the four-variable Modification of Diet in Renal Disease (MDRD) equation [18]. Decisions regarding RRT initiation, discontinuation and modalities were taken by senior nephrologists (E.C., L.Z. and M.D.), based on the guidelines developed by Ronco and Bellomo [19]. Cancer chemotherapy was prescribed by the hematologist in charge of each patient, according to the best standard of care. After hospital discharge, all patients were managed at our hospital, and 6-month follow-up data were available for all of them.

Eligibility criteria

The following malignancies characterized by high sensitivity to chemotherapy were considered in this study: acute myelogenous leukemia (AML), acute lymphoblastic leukemia (ALL) and high-grade non-Hodgkin lymphoma (NHL). High risk of clinical TLS was defined as at least one of the following criteria: bulky tumor (>10 cm), organ infiltration (hepatomegaly, splenomegaly and/or nephromegaly) and peripheral leukocyte count greater than 30.0×10^9/L for AML and 50.0×10^9/L for ALL. Exclusion criteria were prior chronic renal dysfunction, AKI at admission, allopurinol treatment, deficiency of glucose-6-phosphate dehydrogenase (G6PD), no planned cancer chemotherapy and absence of potentially lifespan-extending treatment options.

Treatment designed to decrease risk of clinical TLS

All patients were managed as recommended by recent guidelines [10]. They received the following standardized treatment protocol before chemotherapy initiation: intravenous hydration (2500–3000 mL of normal saline/m^2/day) and urate oxidase (rasburicase, a single intravenous 7.5 mg dose). No patient received allopurinol, loop diuretics or urinary alkalinization. A thorough physical examination including urine output and weight measurements was performed at least once a day. Laboratory tests including plasma potassium, calcium, phosphate, uric acid and creatinine levels were performed every 6 h. Patients who developed clinical TLS were admitted to the ICU. Criteria for initiating RRT were severe AKI (RIFLE Injury or Failure), oliguria ≥ 12 h with fluid overload or uncontrolled metabolic disturbances.

Outcome measurements and follow-up

The data in Tables I and II were collected prospectively. The main outcome measure was the percentage decrease in plasma uric acid level 6 h after a single rasburicase dose ($UA\Delta_{6h}$). $UA\Delta_{6h}$ was calculated as follows: $UA\Delta_{6h} = [(\text{uric acid at admission} - \text{uric acid 6 h after rasburicase}) \times 100]/(\text{uric acid at admission})$. The unit used for uric acid was μmol/L. The main study objective was to determine whether $UA\Delta_{6h}$ correlated with the development of AKI within 7 days following cancer chemotherapy initiation.

Plasma uric acid levels were measured before the rasburicase dose, 6 h and 12 h later, then every 12 h for 96 h. AKI stage was defined as the worst RIFLE stage. Great care was taken to identify all exposures to nephrotoxic agents (e.g. radiographic contrast media, aminoglycosides and non-steroidal anti-inflammatory drugs). Vital status 6 months after hospital discharge was available for all patients. Plasma creatinine levels at hospital discharge and 3 and 6 months after hospital discharge were available.

Statistical analysis

Results are reported as median [interquartile range, IQR] or number (%) or figure 2 gives mean ± SE to express percentage changes. Categorical variables were compared using Fisher's exact test or χ^2 test as appropriate and continuous variables using the non-parametric Wilcoxon test or the Mann–Whitney test for pairwise comparisons.

To evaluate whether $UA\Delta_{6h}$ predicted AKI development, we plotted the receiver operating characteristic (ROC) curves of the proportion of true positives against the proportion of false positives, depending on the prediction rule used to classify patients as having AKI. A 2×2 table was established to determine the sensitivity and specificity of $UA\Delta_{6h}$ for predicting AKI. Cut-off values, defined as threshold values that maximized the sum of sensitivity and specificity, were determined on the ROC curves. The positive and negative likelihood ratios (LR+ and LR−, respectively) were computed.

To further assess the ability of $UA\Delta_{6h}$ to predict AKI, we performed logistic regression analyses to identify variables significantly associated with AKI as measured by odds ratios (ORs) with their 95% confidence intervals (CIs). Variables yielding *p*-values lower than 0.20 in the bivariate analyses were entered into a forward stepwise logistic regression model where AKI was the variable of interest. The covariates were entered into the model with critical entry and removal *p*-values of 0.2 and 0.1, respectively. Collinearity and interactions were tested. The Hosmer–Lemeshow test was used to check goodness-of-fit of the logistic regression model.

All tests were two-sided, and *p*-values <0.05 were considered statistically significant. Statistical tests were performed

Table I. Characteristics of the 62 study patients at hospital admission*.

Variable	All patients ($n = 62$)	AKI ($n = 41$)	No AKI ($n = 21$)	p-Value
Demographics				
Age (years)	48 [31;61]	49 [27;59]	41 [31;69]	0.58
Weight (kg)	72 [60;83]	72 [61;83]	69 [60;72]	0.16
Male gender	37 (59.7)	27 (65.8)	10 (47.6)	0.18
Co-morbidities				
Hypertension	11 (17.7)	10 (24.4)	1 (4.7)	0.08
Heart failure	7 (11.3)	6 (14.6)	1 (4.7)	0.40
Diabetes mellitus	5 (8)	4 (9.7)	1 (4.7)	0.65
Hematological malignancy				
Non-Hodgkin lymphoma	31 (50)	19 (46.4)	12 (57.1)	0.52
Acute myelogenous leukemia	17 (27.4)	11 (26.8)	6 (28.6)	
Acute lymphoblastic leukemia	14 (22.6)	11 (26.8)	3 (14.3)	
Laboratory data at admission				
Leukocyte count ($\times 10^9$/L)	16.1 [6.7;109.5]	25.0 [7.2;149.0]	14.2 [6.7;55.5]	0.21
DIC	13 (21)	11 (26.8)	2 (9.5)	0.18
Plasma creatinine (µmol/L)	76 [64;90]	78 [67;91]	67 [58;82]	0.08
eGFR (mL/min/1.73 m^2)	90 [74;110]	85 [72;116]	93 [89;102]	0.26
Lactate dehydrogenase (U/L)	2274 [1005;4783]	3465 [1569;4804]	1217 [752;2075]	<0.01
Calcemia (mmol/L)	2.23 [2.03;2.33]	2.25 [2.0;2.33]	2.2 [2.12;2.32]	0.52
Phosphatemia (mmol/L)	1.21 [0.95;1.65]	1.35 [0.97;1.7]	1.07 [0.94;1.38]	0.23
Uric acid (µmol/L)	443 [320;605]	511 [382;589]	418 [265;518]	0.04
Response to rasburicase				
Uric acid 6 h after rasburicase (µmol/L)	42 [12;104]	64 [16;157]	14 [12;33]	<0.01
$UA\Delta_{6h}$	91 [76;97]	84 [65;95]	95 [92.3;97.8]	<0.01
Chemotherapy	62 (100)	41 (100)	21 (100)	
Exposure to nephrotoxic agents				
Radiographic contrast agents	24 (38.7)	15 (36.5)	9 (42.8)	0.78
Aminoglycosides	16 (25.8)	14 (34.1)	2 (9.5)	0.06
Non-steroidal anti-inflammatory drugs	4 (6.4)	4 (9.7)	0 (0)	0.29
Outcome data				
Hospital length of stay (days)	34 [16;43]	36 [23;48]	30 [9;39]	0.17
Hospital mortality	11 (17.7)	11 (26.8)	0 (0)	0.01
6-Month mortality	19 (30.6)	17 (41.4)	2 (9.5)	0.04

IQR, interquartile range; AKI, acute kidney injury; DIC, disseminated intravascular coagulopathy; eGFR, estimated glomerular filtration rate according to Modification of Diet in Renal Disease; $UA\Delta_{6h}$, percentage decrease in plasma uric acid 6 h after single 7.5 mg rasburicase dose.
*Results are given as n (%) or median [IQR].

with SPSS 13.0 (IBM, Armonk, NY) and Statview 5.0 (SAS Institute, Cary, NC) software packages.

Results

Patients

During the study period, 62 patients admitted to the Saint-Louis University Hospital were at high risk for clinical TLS. The flowchart is shown in Figure 1 and patient characteristics in Table I. Patients with and without subsequent AKI showed no significant differences for age, gender or comorbidities. The distribution of hematological malignancies was similar in these two groups, but patients who developed AKI had higher levels of markers for tumor burden (lactate dehydrogenase and uric acid).

At admission, none of the patients had renal disease or renal failure. Median plasma creatinine was 76 µmol/L [64;90], indicating an eGFR of 90 mL/min per 1.73 m^2 [74;110]. The groups with and without subsequent AKI showed no significant differences for the other metabolic parameters, including plasma potassium, calcium and phosphate, and leukocyte count.

Clinical tumor lysis syndrome

All patients received intravenous hydration with normal saline and a single 7.5 mg rasburicase dose (0.11 mg/kg [0.09;0.12]) before cancer chemotherapy initiation. No drug-related life-threatening events or deaths occurred during the study. All cases of clinical TLS were defined by the occurrence of AKI. No patient experienced cardiac dysrhythmia, fatal hyperkalemia, seizures or neuromuscular irritability.

Of the 62 patients, 41 (66.1%) fulfilled criteria for AKI, 1 day [1;2] after cancer chemotherapy initiation. Among them 46.3% were in the Risk category, 19.5% in the Injury category and 34.1% in the Failure category of the RIFLE classification scheme (Table II). RRT was used in 28 (68.3%) patients with AKI, for a median of 3 days [2;5]. Among the 28 patients treated by RRT, AKI stage Injury or Failure was the main reason for 17 (61%) patients, and uncontrolled metabolic disorders associated with AKI stage Risk was the main reason for 11 (39%) patients. RRT modalities were intermittent hemodialysis (75%) and continuous veno-venous hemofiltration (25%). All survivors had normal renal function 3 months after hospital discharge. AKI was associated with higher hospital and 6-month mortality rates (Table I).

Plasma uric acid response rate to rasburicase and prediction of AKI

$UA\Delta_{6h}$ was significantly greater in patients who did not develop AKI than in those who did (95% vs. 84%; $p < 0.01$). The time-course of plasma uric acid levels is shown in

Table II. Characteristics of acute kidney injury ($n = 41$).

Variable	n (%) or median [IQR]
Time from chemotherapy to AKI (days)	1 [1;2]
RIFLE classification*	
Risk, n (%)	19 (46.3)
Plasma creatinine (µmol/L)	82 [73;93]
RRT, n (%)	11 (57)
Injury, n (%)	8 (19.5)
Plasma creatinine (µmol/L)	94 [84;114]
RRT, n (%)	4 (50)
Failure, n (%)	14 (34.1)
Plasma creatinine (µmol/L)	101 [82;159]
RRT, n (%)	13 (93)
Oliguria	13 (31.7)
RRT modalities	28 (68.3)
Intermittent hemodialysis	21 (75)
Continuous veno-venous hemofiltration	7 (25)
Duration of RRT (days)	3 [2;5]
Follow-up data on renal function	
Plasma creatinine (µmol/L) at hospital discharge in RRT-free patients	53 [41;62]
Plasma creatinine (µmol/L) at month 3	51 [47;67]
Plasma creatinine (µmol/L) at month 6	60 [47;72]
Renal recovery at month 3 among survivors ($n = 29$)	29 (100)

IQR, interquartile range; AKI, acute kidney injury; RRT, renal replacement therapy.
*RIFLE: classification scheme for acute kidney injury (AKI). The classification system includes separate criteria for creatinine (Creat) and urine output (UO). A patient can fulfill the criteria through changes in Creat, changes in UO or both. The criteria that lead to the worst possible classification should be used. R, RIFLE Risk category: 1.5-fold Creat increase or $>25\%$ glomerular filtration rate (GFR) decrease or UO <0.5 mL/kg/h for 6 h. I, RIFLE Injury category: 2-fold Creat increase or $>50\%$ GFR decrease or UO <0.5 mL/kg/h for 12 h. F, RIFLE Failure category: 3-fold Creat increase or Creat greater than 4.0 mg/dL (350 µmoL/L) with an acute increase of at least 0.5 mg/dL (44 µmol/L) or $>75\%$ GFR decrease or UO <0.3 mL/kg/h for 24 h, or anuria for 12 h.

Figure 2. Patients who developed AKI had higher baseline plasma uric acid levels and smaller $UA\Delta_{6h}$ values.

Figure 3 shows the area under the ROC curve (AUC-ROC) for the AKI prediction model. A $UA\Delta_{6h}$ value lower than 92.9% 6 h after the single 7.5 mg rasburicase dose predicted AKI (AUC-ROC, 0.74; 95% CI, 0.61–0.85). In a multivariate model where AKI was the variable of interest, hypertension and $UA\Delta_{6h} < 92.9\%$ were independently associated with AKI (Table III).

Discussion

This study was designed to evaluate the ability of a routine bedside laboratory test to predict the development of AKI in patients at high risk for clinical TLS. In our study population, two-thirds of patients developed clinical TLS, which was consistently defined by the occurrence of AKI. The plasma uric acid response 6 h after a single rasburicase dose ($UA\Delta_{6h}$) given before cancer chemotherapy initiation was significantly greater in patients without AKI compared to patients who developed AKI. $UA\Delta_{6h}$ lower than 92.9% predicted AKI with 70% sensitivity and 71% specificity. Hypertension and $UA\Delta_{6h}$ lower than 92.9% were independently associated with AKI. These data suggest that early ICU admission of patients with low $UA\Delta_{6h}$ values might improve survival.

TLS is a well-known life-threatening emergency encountered in patients with hematological malignancies. Metabolic disturbances due to the release of tumor cell contents into the bloodstream can induce AKI [20]. Although

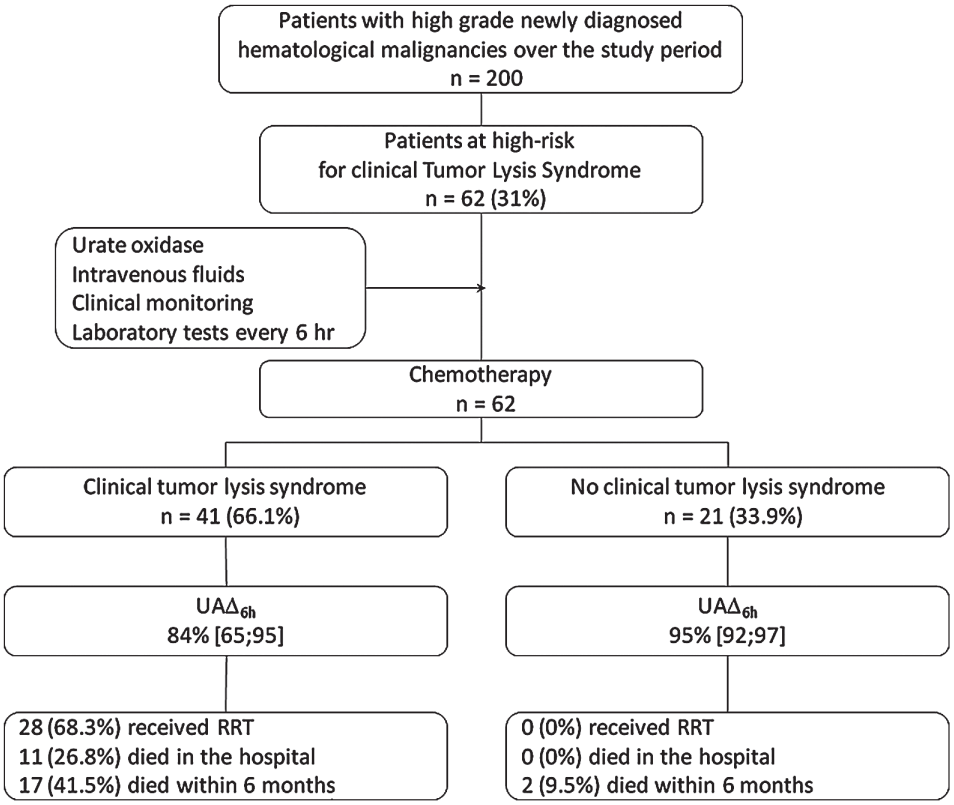

Figure 1. Flowchart of 62 patients with hematological malignancies at high risk for tumor lysis syndrome included in the study. RRT, renal replacement therapy; $UA\Delta_{6h}$, percentage decrease in plasma uric acid 6 h after single 7.5 mg rasburicase dose.

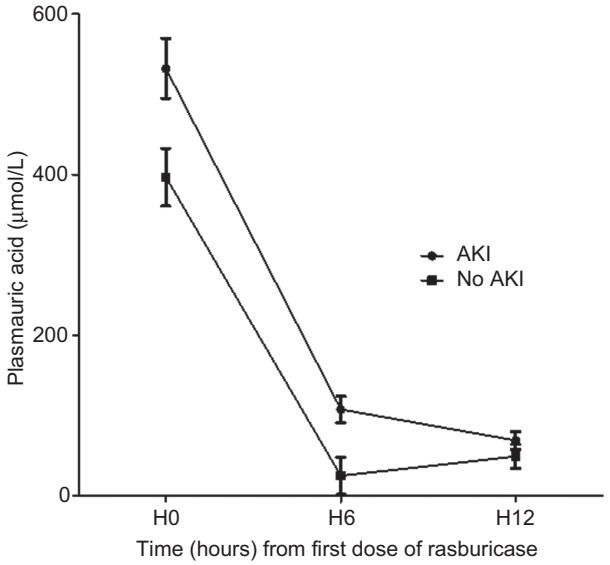

Figure 2. Mean (± SE) plasma uric acid concentrations over time (h) in the overall study population. Circles denote patients who developed acute kidney injury (AKI) ($n = 41$) and squares those who did not ($n = 21$). The 6 and 12 h levels are those measured 6 and 12 h after 7.5 mg rasburicase dose given before chemotherapy initiation. Patients who developed AKI had higher plasma uric acid levels 6 h after rasburicase. Uric acid at admission ($p = 0.04$) and 6 h after rasburicase ($p < 0.01$) were compared between AKI and non-AKI group using Mann–Whitney test.

guidelines for TLS management were issued recently, the optimal method for assessing the risk of clinical TLS in individual patients remains unclear [1,10,11]. The reported incidence of TLS ranged from 3 to 30% depending on the numerator (laboratory TLS, clinical TLS or both), denominator (all, low-risk, intermediate-risk or high-risk patients) and type of chemotherapy [4,5,21–28]. The impact of laboratory TLS on morbidity and mortality is unclear. In contrast, clinical TLS, of which the most common defining symptom is

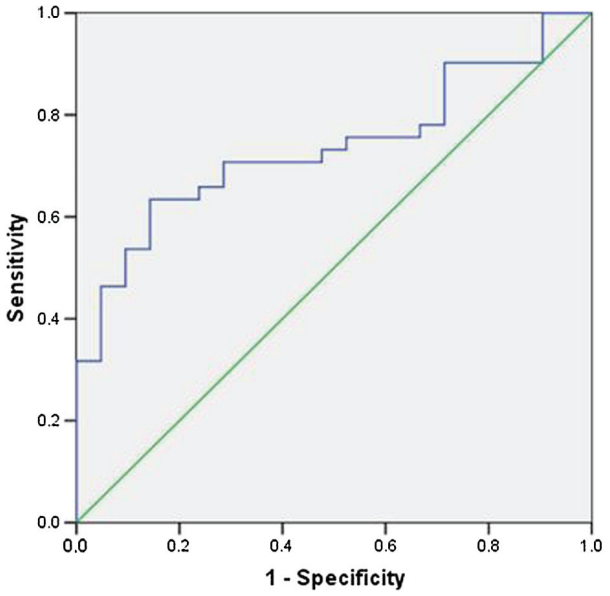

Figure 3. Receiver operating characteristic (ROC) curve for model predicting clinical tumor lysis syndrome. A reduction in plasma uric acid < 92.9% 6 h after single intravenous 7.5 mg dose of rasburicase predicted clinical tumor lysis syndrome. Area under the curve is 0.74 (0.61–0.85).

Table III. Multivariate analysis: predictors of clinical tumor lysis syndrome*.

	Odds ratio	95% Confidence interval	*p*-Value
$UA\Delta_{6h} < 92.9\%$	8.90	[2.3;33.4]	< 0.01
Hypertension	11.4	[1.1;116.8]	0.04
Exposure to aminoglycoside	5.26	[0.8;31.4]	0.06

$UA\Delta_{6h}$, percentage decrease in plasma uric acid 6 h after single 7.5 mg rasburicase dose.
*Candidate predictors were $UA\Delta_{6h} < 92.9\%$ after a single 7.5 mg rasburicase dose, aminoglycoside exposure and hypertension. Hosmer and Lemeshow test: $\chi^2 = 5.15$; df = 4; $p = 0.88$.

AKI, is associated with increases in healthcare costs, hospital stay length and mortality [6]. We focused on patients at high risk for clinical TLS, using the RIFLE classification to define AKI. This explains the high incidence of clinical TLS, of 66.1%. In accordance with previous studies, all patients with clinical TLS required ICU admission and two-thirds of them required RRT. Hospital mortality was higher in patients with versus without clinical TLS ($p = 0.01$) [2,5,29].

Among our patients at high risk, one-third did not develop clinical TLS. The better rasburicase response in these patients compared to those who developed AKI may be related to at least two factors. First, baseline plasma uric acid was higher in the AKI group, indicating a greater tumor burden and therefore the potential for a larger amount of uric acid being released into the bloodstream. Second, in clinical practice AKI is defined by changes in plasma creatinine, which are used as a surrogate for changes in GFR. However, plasma creatinine is of limited value for the early detection of renal injury. Conceivably, a smaller response to rasburicase may indicate subclinical AKI at presentation, with a decrease in uric acid clearance. This subclinical AKI may be related to hyperuricemia and other contributing factors (calcium phosphate and oxalate intrarenal crystallization, exposure to nephrotoxic drugs). An evaluation of early biomarkers (neutrophil gelatinase-associated lipocalin, kidney injury molecule-1, cystatin C and interleukin-18) might be of use to confirm this hypothesis.

$UA\Delta_{6h}$ lower than 92.9% had 70% sensitivity and 71% specificity for predicting subsequent AKI. In the multivariate analysis, $UA\Delta_{6h}$ lower than 92.9% and hypertension independently predicted AKI. This early prediction model may assist in identifying patients at high risk for AKI who may benefit from closer monitoring, early ICU admission, early RRT and low-intensity initial cancer chemotherapy.

To our knowledge, only three scoring systems for predicting TLS have been reported so far [21–23]. However, TLS management in these three studies did not include rasburicase as recommended by guidelines in patients at high risk. In addition, these studies used a retrospective design, included only patients with AML or ALL, used different definitions of TLS and measured different outcomes (laboratory or clinical TLS).

Our study has several limitations. Given the single-center design, the characteristics of our institution may have influenced the results. However, the definitions, risk assessment method and TLS management complied with international guidelines. Thus, our results may also apply to other settings.

The small sample size resulted in limited statistical power, which precluded the inclusion of other markers in the multivariate analysis. However, TLS is relatively uncommon, and we elected to focus on the clinically relevant high-risk population and on the outcome of interest for everyday practice. The strengths of our study include the homogeneous patient population recruited over a short period (3 years) during which no changes in treatment practices occurred. Also, our ICU has extensive experience in managing medical complications of hematological malignancies [16,30–33].

In summary, our findings provide a piece of the puzzle that will help understand actual risk for AKI in patients with high-risk hematological malignancies. Thus, the response to rasburicase provides some information on the risk of AKI, but needs to be combined with other factors such as the use of nephrotoxic agents, hypotension and renal infiltration by the malignancy to better establish a practical approach involving a simple risk-prediction model for AKI in patients at high risk for clinical TLS. Studies in larger cohorts are needed before practical recommendations to assist in patient management can be established.

Potential conflict of interest: Disclosure forms provided by the authors are available with the full text of this article at www.informahealthcare.com/lal.

References

[1] Howard SC, Jones DP, Pui CH. The tumor lysis syndrome. N Engl J Med 2011;364:1844–1854.

[2] Candrilli S, Bell T, Irish W, et al. A comparison of inpatient length of stay and costs among patients with hematologic malignancies (excluding Hodgkin disease) associated with and without acute renal failure. Clin Lymphoma Myeloma 2008;8:44–51.

[3] Stapleton FB, Strother DR, Roy S 3rd, et al. Acute renal failure at onset of therapy for advanced stage Burkitt lymphoma and B cell acute lymphoblastic lymphoma. Pediatrics 1988;82:863–869.

[4] Bowman WP, Shuster JJ, Cook B, et al. Improved survival for children with B-cell acute lymphoblastic leukemia and stage IV small noncleaved-cell lymphoma: a pediatric oncology group study. J Clin Oncol 1996;14:1252–1261.

[5] Darmon M, Guichard I, Vincent F, et al. Prognostic significance of acute renal injury in acute tumor lysis syndrome. Leuk Lymphoma 2010;51:221–227.

[6] 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;44:77–83.

[7] Hochberg J, Cairo MS. Tumor lysis syndrome: current perspective. Haematologica 2008;93:9–13.

[8] Andreoli SP, Clark JH, McGuire WA, et al. Purine excretion during tumor lysis in children with acute lymphocytic leukemia receiving allopurinol: relationship to acute renal failure. J Pediatr 1986;109:292–298.

[9] Shimada M, Johnson RJ, May WS Jr, et al. A novel role for uric acid in acute kidney injury associated with tumour lysis syndrome. Nephrol Dial Transplant 2009;24:2960–2964.

[10] Coiffier B, Altman A, Pui CH, et al. Guidelines for the management of pediatric and adult tumor lysis syndrome: an evidence-based review. J Clin Oncol 2008;26:2767–2778.

[11] Cairo MS, Bishop M. Tumour lysis syndrome: new therapeutic strategies and classification. Br J Haematol 2004;127:3–11.

[12] Brogard JM, Coumaros D, Franckhauser J, et al. Enzymatic uricolysis: a study of the effect of a fungal urate-oxydase. Rev Eur Etud Clin Biol 1972;17:890–895.

[13] 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 2001;97:2998–3003.

[14] Legoux R, Delpech B, Dumont X, et al. Cloning and expression in Escherichia coli of the gene encoding Aspergillus flavus urate oxidase. J Biol Chem 1992;267:8565–8570.

[15] Cheuk DK, Chiang AK, Chan GC, et al. Urate oxidase for the prevention and treatment of tumor lysis syndrome in children with cancer. Cochrane Database Syst Rev 2010;CD006945.

[16] Thiery G, Azoulay E, Darmon M, et al. Outcome of cancer patients considered for intensive care unit admission: a hospital-wide prospective study. J Clin Oncol 2005;23:4406–4413.

[17] Bellomo R, Ronco C, Kellum JA, et al. Acute renal failure - definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. Crit Care 2004;8:R204–R212.

[18] Hemmelgarn BR, Clement F, Manns BJ, et al. Overview of the Alberta Kidney Disease Network. BMC Nephrol 2009;10:30.

[19] Bellomo R, Ronco C. Indications and criteria for initiating renal replacement therapy in the intensive care unit. Kidney Int Suppl 1998;66:S106–S109.

[20] Davidson MB, Thakkar S, Hix JK, et al. Pathophysiology, clinical consequences, and treatment of tumor lysis syndrome. Am J Med 2004;116:546–554.

[21] Montesinos P, Lorenzo I, Martin G, et al. Tumor lysis syndrome in patients with acute myeloid leukemia: identification of risk factors and development of a predictive model. Haematologica 2008;93:67–74.

[22] Mato AR, Riccio BE, Qin L, et al. A predictive model for the detection of tumor lysis syndrome during AML induction therapy. Leuk Lymphoma 2006;47:877–883.

[23] Truong TH, Beyene J, Hitzler J, et al. Features at presentation predict children with acute lymphoblastic leukemia at low risk for tumor lysis syndrome. Cancer 2007;110:1832–1839.

[24] Cairo MS, Gerrard M, Sposto R, et al. Results of a randomized international study of high-risk central nervous system B non-Hodgkin lymphoma and B acute lymphoblastic leukemia in children and adolescents. Blood 2007;109:2736–2743.

[25] Cortes J, Moore JO, Maziarz 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;28:4207–4213.

[26] Patte C, Sakiroglu C, Ansoborlo S, et al. Urate-oxidase in the prevention and treatment of metabolic complications in patients with B-cell lymphoma and leukemia, treated in the Societe Francaise d'Oncologie Pediatrique LMB89 protocol. Ann Oncol 2002;13:789–795.

[27] 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.

[28] Pui CH, Jeha S, Irwin D, et al. Recombinant urate oxidase (rasburicase) in the prevention and treatment of malignancy-associated hyperuricemia in pediatric and adult patients: results of a compassionate-use trial. Leukemia 2001;15:1505–1509.

[29] Cohen LF, Balow JE, Magrath IT, et al. Acute tumor lysis syndrome. A review of 37 patients with Burkitt's lymphoma. Am J Med 1980;68:486–491.

[30] Azoulay E, Mokart D, Lambert J, et al. Diagnostic strategy for hematology and oncology patients with acute respiratory failure: randomized controlled trial. Am J Respir Crit Care Med 2010;182:1038–1046.

[31] Lengline E, Raffoux E, Lemiale V, et al. Intensive care unit management of patients with newly diagnosed acute myeloid leukemia with no organ failure. Leuk Lymphoma 2012;53:1352–1359.

[32] Legrand M, Max A, Peigne V, et al. Survival in neutropenic patients with severe sepsis or septic shock. Crit Care Med 2012;40:43–49.

[33] Darmon M, Ciroldi M, Thiery G, et al. Clinical review: specific aspects of acute renal failure in cancer patients. Crit Care 2006;10:211.

Supplementary material available online

Definition of clinical TLS and criteria used to assess risk of TLS