Tumor lysis syndrome in patients with acute myeloid leukemia: identification of risk factors and development of a predictive model

Pau Montesinos, Ignacio Lorenzo, Guillermo Martín, Jaime Sanz, Maria Luz Pérez-Sirvent, David Martínez, Guillermo Ortí, Lorenzo Algarra, Jesus Martínez, Federico Moscardó, Javier de la Rubia, Isidro Jarque, Guillermo Sanz, and Miguel A. Sanz

Hematology Service, Hospital Universitario La Fe, Valencia, Spain

Funding: this work was supported by a grant (nº 2006/0137) from the "Fundación para la Investigación Hospital Universitario La Fe, Ayudas Bancaja".

Acknowledgments: we would like to thank Carlos Pastorini and Miguel Priego for excellent technical assistance with the database management.

Manuscript received March 30, 2007.
Manuscript accepted October 16, 2007.

Correspondence:
Miguel Ángel Sanz, Servicio de Hematología, Hospital Universitario La Fe, Avenida Campanar 21, 46019, Valencia, Spain.
E-mail: msanz@uv.es

ABSTRACT

Background
Despite the prophylactic use of allopurinol, tumor lysis syndrome (TLS)- related morbidity and mortality still occur in a number of patients with acute myeloid leukemia (AML). The aim of this study was: (i) to analyze the incidence and outcome of TLS in a large series of patients with AML receiving hyperhydration and allopurinol, (ii) to identify risk factors for TLS, and (iii) to develop a prognostic scoring system for estimating individual risk of TLS.

Design and Methods
The study included 772 adult patients with AML receiving induction chemotherapy between 1980 and 2002. TLS was divided into laboratory TLS (LTLS) or clinical TLS (CTLS). The population study was randomly divided into training and test subsets, so that a prognostic model for CTLS was developed in one set and validated in the other.

Results
Overall, 130 patients (17%) developed TLS (5% CTLS and 12% LTLS). Unlike LTLS, CTLS was associated with a higher rate of death from induction therapy. Multivariate analysis showed that pretreatment serum lactate dehydrogenase (LDH) levels above laboratory normal values, creatinine >1.4 mg/dL, uric acid >7.5 mg/dL and white blood cell (WBC) counts >25×10^9/L were independent risk factors for CTLS and LTLS. The scoring system, based on pretreatment WBC counts, and uric acid and LDH serum levels, had excellent discrimination and was accurate for predicting CTLS and LTLS.

Conclusions
TLS is frequently observed in AML patients during induction therapy. Only the development of CTLS had an impact on higher mortality rate from induction therapy. The scoring system derived from this study can be used to obtain an accurate estimate of the individual risk of TLS, allowing for risk-adapted prophylaxis against this complication.

Key words: tumor lysis syndrome, acute myeloid leukemia, incidence, risk factors, predictive model.

Citation: Montesinos P, Lorenzo I, Martín G, Sanz J, Pérez-Sirvent ML, Martínez D, Ortí G, Algarra L, Martínez J, Moscardó F, de la Rubia J, Jarque I, Sanz G, Sanz MA. Tumor lysis syndrome in patients with acute myeloid leukemia: identification of risk factors and development of a predictive model. Haematologica. 2008 Jan; 93:(1)67-74. DOI: 10.3324/haematol.11575

Introduction

Tumor lysis syndrome (TLS) can be a life-threatening complication during induction chemotherapy in patients with acute leukemia. TLS is characterized by hyperuricemia, hyperkalemia, hyperphosphatemia, hypocalcemia and acute renal failure. These abnormalities may occur spontaneously before the initiation of chemotherapy due to increased catabolism and the turn-over of leukemic cells,[1-3] but more frequently TLS is induced by intensive chemotherapy. Acute urate nephropathy is the main cause of renal failure during TLS, but calcium phosphate precipitation may also contribute to impaired renal function.[4] The standard management of TLS includes generous hyperhydration, urine alkalinization and uric acid reduction with allopurinol. Despite these measures, TLS-related morbidity and mortality still occur in a sizeable proportion of patients with hematologic malignancies.[5-7] However, few studies on TLS are focused on patients with acute myeloid leukemia (AML), and the incidence and outcome of TLS in this population is not well defined.[8,9] With the introduction into clinical practice of new agents, such as recombinant urate oxidase (rasburicase),[10] for the prevention or treatment of TLS, there has been an increased interest in defining the population at high risk of TLS. As TLS is thought to be uncommon in AML, risk factors for TLS have been extrapolated to AML from studies performed in patients with lymphoid malignancies.[6,11,12] Therefore, efforts to define the specific risk factors for TLS in patients with AML are required. We performed a single-center retrospective chart review study with the aim of: (i) analyzing the incidence, characteristics and outcome of TLS in a large series of patients with AML homogeneously managed with hyperhydration and allopurinol, (ii) identifying risk factors for the development of TLS in patients with AML, and (iii) developing a new, simple scoring system for routine clinical use, allowing for risk-adapted management of this complication.

Design and Methods

Patients

This study included all adult patients (>13 years) admitted to a single institution with a diagnosis of AML and treated with intensive chemotherapy between January 1980 and December 2002. The institutional review board of *La Fe* University Hospital approved the study. Three patients, who received rasburicase in the context of a clinical trial between 2001 and 2002, were excluded from the study. AML was diagnosed and classified according to the French-American-British (FAB) criteria.[13] Differential blood counts and biochemistry tests including levels of creatinine, urea, calcium, phosphate, potassium and uric acid were performed in all patients at diagnosis, on day 1 of chemotherapy (baseline) and every 1–3 days during hospitalization for induction therapy.

Data collection

Baseline blood and serum laboratory values were prospectively collected. These included white blood cell (WBC) count, platelet count, hemoglobin, glucose, creatinine, urea, calcium, phosphate, potassium, uric acid, lactate dehydrogenase (LDH), glutamate oxaloacetate transferase (GOT), glutamate pyruvate transferase (GPT), total bilirubin and fibrinogen levels, as well as prothrombin time. Physical examination data on admission included weight, height, performance status using Eastern Cooperative Oncology Group (ECOG) criteria, hemorrhagic syndrome, fever and the presence of hepatomegaly, splenomegaly or lymphadenopathy.

For the diagnosis of TLS, clinical records were retrospectively reviewed by a single investigator (PM). The clinical data examined included the following biochemical values collected throughout hospitalization for induction therapy: creatinine, urea, calcium corrected for total protein, phosphate, potassium and uric acid. The development of oliguria or other complications attributable to TLS and the management of these complications were also assessed.

Chemotherapy regimens

Induction therapy consisted of the classic combination of cytarabine and anthracycline with or without a third agent (50%), cytarabine plus adriamycin and thioguanine or vincristine (18%), monochemotherapy with anthracycline with or without all-trans retinoic acid in patients with acute promyelocytic leukemia (16%), high-dose cytarabine (8%), and other regimens (8%).

Management of TLS

Prophylaxis against TLS consisted of generous intravenous hydration (>2 L/m^2 day) and oral allopurinol (300–600 mg/day). The majority of patients (95%) received prophylaxis with bicarbonate. Diuretics were used for the management of fluid overload. Dialysis was performed for the treatment of oliguric renal failure or life-threatening metabolic disorders.

Definition of TLS

Laboratory TLS (LTLS) was defined as: (i) >25% change from baseline values or the presence of serum levels above normal laboratory values in any two or more of the following parameters: potassium, uric acid, phosphate and calcium; or (iii) serum levels above normal laboratory values (potassium >5 mEq/L, uric acid >7.5 mg/dL, phosphate >5 mg/dL and calcium <8 mg/dL) in at least one of the previously described parameters and creatinine serum levels above 1.4 mg/dL (Table 1). For patients with antecedent of chronic renal failure or chronic hyperuricemia, >25% changes from baseline values of creatinine and uric acid, were required as criteria for LTLS. These criteria had to be met within 3 days before and 7 days after the initiation of chemotherapy in the absence of any other recognizable cause.

Clinical TLS (CTLS) was defined as the presence of LTLS

Table 1. Definition and classification of TLS.

LTLS (A)*	Two or more of the following abnormalities: Uric acid >7.5 mg/dL or 25% increase from baseline Potassium >5 meq/L or 25% increase from baseline Phosphate >5 mg/dL or 25% increase from baseline Calcium <8 mg/dL or 25% decrease from baseline
LTLS (B)*	Creatinine >1.4 mg/dL + ≥1 of the following abnormalities: Uric acid >7.5 mg/dL Potassium >5 meq/L Phosphate >5 mg/dL Calcium <8 mg/dL
CTLS*	LTLS (A) or (B) + one or more of the following clinical complications: Oliguria (urine output ≤800 mL/day) Dialysis Cardiac arrhythmia/sudden death Electrocardiographic signs of hyperkalemia Seizures Tetany

** These criteria must be met within 3 days before and 7 days after the initiation of chemotherapy in the absence of any other recognizable cause. For patients with antecedent of chronic renal failure or chronic hyperuricemia, >25% changes from baseline values of creatinine and uric acid serum levels were required as criteria for LTLS. LTLS: laboratory tumor lysis syndrome; CTLS: clinical tumor lysis syndrome.*

Table 2. Baseline characteristics of the AML patients studied.

Total patients	772
Sex (M/F), n (%)	450/322 (58/42)
Median age, yr (range)	54 (14-80)
FAB subtype, n (%)	
M0	21 (3)
M1	171 (22)
M2	159 (21)
M3	129 (17)
M4	116 (15)
M5	86 (11)
M6	48 (6)
M7	11 (1)
Unclassified	31 (4)
Type of AML	
De novo	663 (86)
Secondary	109 (14)
WBC×10^9/L, n (%)	
≤ 25	504 (65)
25-75	139 (18)
>75	129 (17)
LDH×ULN, n (%)	
≤1	239 (34)
1-4	379 (55)
>4	76 (11)
Uric acid (mg/dL), n (%)	
≤7.5	663 (91)
>7.5	69 (9)
Creatinine (mg/dL), n (%)	
≤1.4	698 (92)
>1.4	64 (8)

ULN: Upper laboratory normal values.

and at least one of the following TLS-related complications in the absence of any other recognizable cause: oliguric renal failure (urine output ≤800 mL/day), hemodialysis, electrocardiographic signs of hyperkalemia, cardiac arrhythmia/sudden death, tetany or seizures.

Statistical analysis

For the univariate analysis, the continuous quantitative variables were transformed into categorical intervals. The prognostic value for each independent variable was analyzed using the χ^2 test and, when needed, Yates' correction test.[14] We considered values of $p<0.05$ to be statistically significant. Statistically significant variables after univariate analysis were included in the multivariate analysis, which was performed using a stepwise logistic regression model.[15] For the purposes of multivariate analysis, groups were divided using the most significant cut-off points obtained in the univariate analysis (Table 3). Binary co-variates (i.e. age, sex and creatinine) were encoded as 0 and 1, and LDH serum levels and WBC count, for which three risk categories were found, were encoded as 0, 1 and 2. Co-variates were entered as interval-scaled variables for the Cox proportional hazards regression analyses.[16]

To validate a predictive model for the prediction of the development of CTLS, we randomly divided the 772 patients into training and test subsets containing 390 and 382 cases, respectively. A prognostic model was developed in the training sample and validated in the test sample.

A multivariate analysis for CTLS was carried out in the training sample. Using regression coefficients to weight each selected co-variate, we obtained a categorical risk score for routine clinical use. This scoring system was validated in the test sample, using the Hosmer-Lemeshow goodness-of-fit test to compare the observed and predicted frequencies. A p value <0.05 indicated that the predicted values did not fit the data.[17] Scoring model discrimination was assessed by using the area under the receiver operating characteristic curve (AUC). AUC values 0.8-0.9 are considered excellent, and >0.9 outstanding.[18] The AUC was calculated for the training sample, the test sample and the total series. Sensitivity and specificity were calculated for the consecutive cut-offs of the sum scores for the training sample, the test sample and the total series. The scoring model discrimination for predicting the development of LTLS was also tested, calculating the AUC for the training sample, the test sample and the total series.

All computations were performed using the 4F and LR programs from the BMDP statistical library (BMDP Statistical Software Inc, Los Angeles, CA, USA).[16] The BMDP special function RNDU was used for the random assignment of cases for the training and test samples.

Results

Patients' characteristics

We studied 772 consecutive adult patients diagnosed with AML who received intensive chemotherapy. The median age of the cohort was 54 years (range, 14–80 years). One hundred and nine patients (14%) had a diagnosis of secondary AML (60 with antecedent of myelodys-

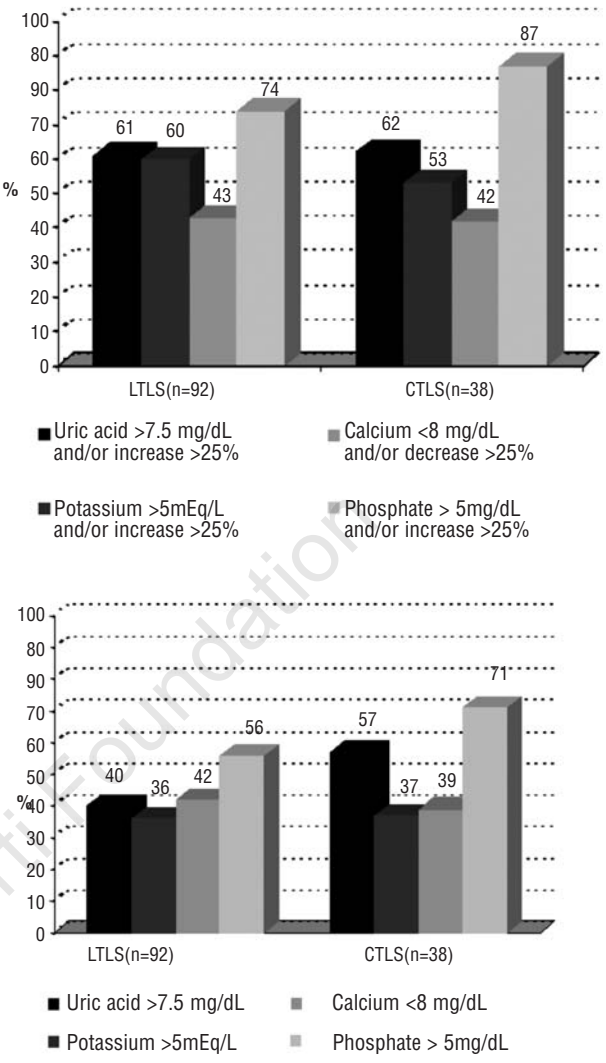
Table 3. Prognostic factors for CTLS and LTLS in the total series. Univariate analysis.

Characteristic	CTLS n (%)	p value	LTLS n (%)	p value
Overall	38/772 (5)		92/734 (12)	
Age (years)				
≤50	9 (3)	0.03 [1]	34 (10)	0.11 [2]
51-60	8 (5)		16 (10)	
61-70	13 (7)		29 (16)	
>70	8 (10)		13 (19)	
Gender				
Male	27 (6)	0.14	55 (13)	0.65
Female	11 (3)		37 (12)	
Type of AML				
De novo	31 (5)	0.59	74 (12)	0.12
Secondary	7 (6)		18 (18)	
WBC (≤10^9/L)				
≤25	7 (1)		20 (4)	
25-75	8 (6)	<0.0001 [3]	30 (23)	<0.0001 [4]
>75	23 (18)		42 (40)	
LDH (×ULN) (n=694)				
≤1	1 (1)		6 (2)	
1-4	21 (5)	<0.0001 [5]	57 (16)	<0.0001 [6]
>4	14 (18)		23 (37)	
Creatinine (mg/dL) (n=762)				
≤1.4	22 (3)	<0.0001	60 (9)	<0.0001
>1.4	15 (23)		32 (65)	
Uric acid (mg/dL) (n=732)				
≤7.5	20 (3)	<0.0001	60 (9)	<0.0001
>7.5	17 (25)		31 (60)	
FAB subtype				
Other	22 (4)	0.03	51 (9)	<0.0001
M4-M5	16 (8)		41 (22)	
Hepatosplenomegaly				
No	11 (2)	<0.0001	53 (9)	<0.0001
Yes	27 (14)		39 (23)	
GOT (UI/L) (n=758)				
≤50	24 (4)	<0.0001	76 (12)	0.05
>50	12 (13)		16 (20)	

[1]Age ≤60 years vs > 60 years, p=0.02,[2] age ≤60 years vs > 60 years, p=0.02,[3] WBC 25-75 vs ≤25×10^9/L, p=0.007; WBC >75 vs 25-75×10^9/L, p=0.004,[4] WBC 25-75 vs ≤25×10^9/L, p<0.0001; WBC >75 vs 25-75 x10^9/L, p=0.005,[5] LDH 1-4 vs ≤1 × ULN, p=0.018; LDH >4 vs 1-4 × ULN, p<0.0001,[6] LDH 1-4 vs ≤1 × ULN, p<0.0001; LDH >4 vs. 1-4 × ULN, p=0.0001. LTLS: laboratory tumor lysis syndrome, CTLS: clinical tumor lysis syndrome. ULN: upper laboratory normal values.

plastic or myeloproliferative syndromes, and 49 with antecedent of other malignancies or treatment with leukemogenic agents).

The median baseline serum creatinine, uric acid and LDH levels were 1 mg/dL (range, 0.28–11.6 mg/dL), 4.2 mg/dL (range, 0.3–15.4 mg/dL) and 1.4× upper laboratory normal value (ULN) (range, 0.1–50×), respectively. The median baseline WBC count was 11×10^9/L (range, 0.5–385.0×10^9/L). The patients' baseline characteristics are listed in Table 2.



Figures 1 and 2. Frequency of laboratory abnormalities in patients with LTLS and CTLS (from day –3 to resolution of TLS).

Incidence and timing of TLS

TLS was observed in 130 patients (17%), of whom 38 (5%) had CTLS and 92 (12%) had LTLS. The median day of onset of TLS was day +2 after the start of chemotherapy (range, –3 to +7). TLS was present before the initiation of chemotherapy in 32 patients (25%) (eight with CTLS and 24 with LTLS), and was induced by chemotherapy in the remaining 98 (75%).

Characteristics of CTLS and LTLS

The most frequent laboratory abnormality was hyperphosphatemia, which was observed in 61% of cases of TLS (71% and 56% of patients with CTLS and LTLS, respectively). Hyperuricemia was observed in 45% of

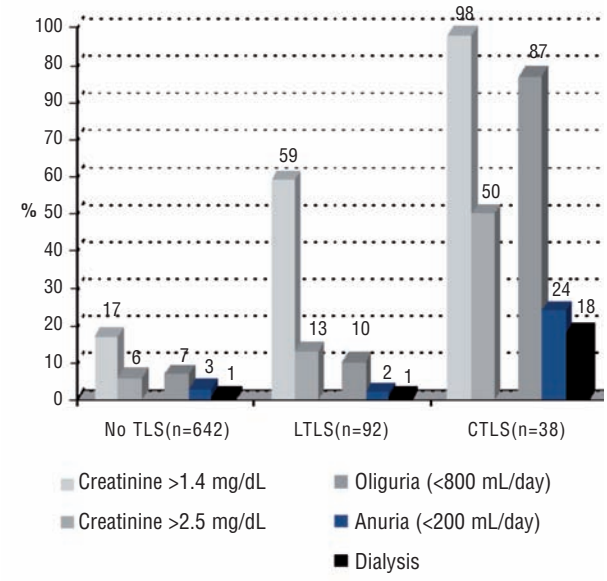


Figure 3. Frequency of clinical renal complications and serum creatinine abnormalities during induction chemotherapy in patients with newly diagnosed AML (oliguria, anuria and dialysis were not due to TLS in all patients with LTLS).

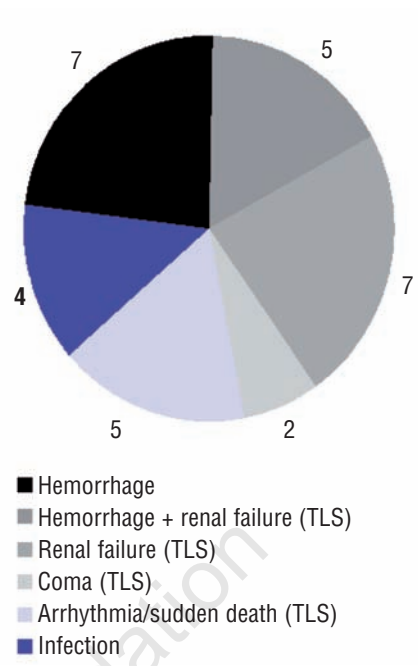


Figure 4. Causes of death during induction chemotherapy in patients with CTLS (n=30/38, 79%).

cases of TLS (in 57% and 40% of patients with CTLS and LTLS, respectively). The frequencies of calcium, phosphate, uric acid and potassium abnormalities defining LTLS and CTLS are shown in Figures 1 and 2. Renal failure, defined as creatinine serum levels above 1.4 mg/dL, occurred in 69% of the patients with TLS (in 98% and 59% of the patients with CTLS and LTLS, respectively). The incidence of renal failure during induction therapy was significantly lower in patients without TLS than in patients with LTLS or CTLS (17% *vs.* 59% *vs.* 98%, $p<0.001$). The incidence of clinical renal complications not attributable to TLS was similar in both patients with and without LTLS (Figure 3).

Oliguria was the main clinical complication defining CTLS and occurred in 33 of 38 patients (87%); dialysis was necessary in seven patients (18%), arrhythmia/sudden death occurred in five patients (13%), seizures/convulsions in four patients (11%) and electrocardiographic signs of hyperkalemia in two patients (5%).

Outcome of CTLS and LTLS

The development of LTLS had no impact on induction death rate (24% *vs.* 22%, $p=0.72$), but CTLS was associated with a higher induction death rate (79% *vs.* 23%, $p<0.001$). The main causes of death in patients with CTLS were hemorrhage and renal failure (Figure 4). CTLS was considered a major cause of death in 19 of the 772 patients (2%).

Table 4. Prognostic factors for CTLS and LTLS in the total series. Multivariate analysis.

Covariate	*Unfavorable categories*	*CTLS*	*p value*	*LTLS*	*p value*
		Odds ratio (95% CI)		*Odds ratio (95% CI)*	
WBC	≤25x10⁹/L	1	<0.001	1	<0.001
	25-75x10⁹/L	2.4 (1.5-3.8)		3.1 (2.1-4.2)	
	>75x10⁹/L	5.8 (2.2-14.4)		9.6 (4.4-17.6)	
Uric acid	≤7.5 mg/dL	1	<0.001	1	<0.001
	>7.5 mg/dL	3.5 (1.5-8.2)		5.7 (2.6-12.7)	
LDH	≤1x ULN	1	0.003	1	0.001
	1-4x ULN	2.5 (1.3-4.8)		2.3 (1.4-3.9)	
	>4x ULN	6.2 (1.7-23.1)		5.3 (1.9-15.2)	
Creatinine	≤1.4 mg/dL	1	0.019	1	<0.001
	>1.4 mg/dL	2.9 (1.6-6.8)		10.7 (4.5-25.1)	

LTLS: laboratory tumor lysis syndrome, CTLS: clinical tumor lysis syndrome.

Prognostic factors for CTLS and LTLS in the whole series

Univariate analysis showed that CTLS was significantly associated with old age, with 60 years being the most significant cut-off point, M4–M5 FAB subtypes, hepatosplenomegaly, GOT >50 UI/L, creatinine >1.4 mg/dL, uric acid >7.5 mg/dL, WBC count >75 *vs.* 25–75 *vs* ≤25×10^9/L and LDH levels >4 *vs.* 1–4 *vs.* ≤1×ULN (Table 3).

LTLS was significantly associated with old age, with 60 years as the most significant cut-off point, M4–M5 FAB subtypes, hepatosplenomegaly, creatinine >1.4 mg/dL, uric acid >7.5 mg/dL, WBC >75 *vs.* 25–75 *vs.* ≤25×10^9/L and LDH levels >4 *vs.* 1–4 *vs.* ≤1×ULN (Table 3).

Multivariate analysis showed that pretreatment WBC count and creatinine, uric acid and LDH levels had independent prognostic value for CTLS and LTLS (Table 4).

Development of the scoring system for CTLS in the training sample

In the training sample, multivariate analysis showed that pretreatment WBC counts, uric acid and LDH serum levels had independent prognostic values for CTLS (Table 5). The AUC of the logistic regression model was 0.91 (95% bias corrected confidence interval (CI), 0.88 to 0.93).

Based on the regression coefficients of the multivariate analysis for each prognostic co-variate, a CTLS scoring system was established. Final risk variables and corresponding scores are listed in Table 5. The predicted probabilities for CTLS according to the sum scores were 0.2%, 0.9%. 2.7%, 7.9%, 20.5%, 43.6% and 69.9% in patients with 0, 1, 2, 3, 4, 5 and 6 points, respectively (Table 6).

The discrimination on the basis of the score was as good as the discrimination of the logistic regression model (AUC 0.90, 95% bias-corrected CI, 0.87 to 0.94). Using cut-off levels of 2, 3, 4 and 5 points, the sensitivity of the model was 95%, 89%, 68% and 42%, respectively. Using cut-off levels of 2, 3, 4 and 5 points, the specificity of the model was 67%, 80%, 92% and 98%, respectively.

Table 5. Prognostic factors for CTLS in the training sample. Multivariate analysis and risk scores.

Co-variate	*Unfavorable categories*	*Regression coefficient*	*CTLS*	*p value*	*Score*
			Odds ratio (95% CI)		
WBC	≤25×10^9/L	1.1	1	<0.001	0
	25-75×10^9/L		2.7 (1.4-5.4)		1
	>75×10^9/L		7.3 (2.0-29.1)		2
Uric acid	≤7.5 mg/dL	2.2	1	<0.001	0
	>7.5 mg/dL		9.1 (3.3-26.6)		1
LDH	≤1×ULN	1.2	1	0.005	0
	1-4×ULN		3.9 (1.5-10.8)		1
	>4×ULN		15.2 (2.2-96.8)		2

LTLS: laboratory tumor lysis syndrome; CTLS: clinical tumor lysis syndrome.

Validation of the scoring system for CTLS in the test sample

In the test sample, the AUC for the scoring model was 0.81 (95% bias-corrected CI, 0.77 to 0.84). The Hosmer-Lemeshow statistic was not significant (χ^2=7.6; p=0.18; 5 *df*), which indicates little departure from a perfect fit. The observed probabilities for CTLS according to the scoring system in the test sample are shown in Table 6.

Application of the scoring system in the whole series

The AUC of the scoring model was 0.87 (95% bias-corrected CI, 0.85 to 0.89), which indicates an excellent model discrimination. The observed probabilities for CTLS and the distribution of patients according to the scoring categories in the whole series are shown in Table 6.

The CTLS scoring system was also able to correctly predict the occurrence of LTLS. The LTLS discrimination on the basis of the sum score was as good as the discrimination for CTLS (the AUC were 0.84, 0.89 and 0.87 in the training sample, the test sample and the total series, respectively).

Table 6. Predicted probabilities for CTLS according to the sum scores in the training set, and observed probabilities in the test set and the whole series.

	Training Set[a] (n=344)	*Test Set[a] (n=323)*	*Whole Series[a] (n=667)*	
Score (points sum)	*Predicted probability of CTLS (%)*	*Observed probability of CTLS (%)*	*Observed probability of CTLS (%)*	*Total number of patients N (%)*
0	0.2	0	0	192 (29)
1	0.9	1.8	1.4	223 (33)
2	2.7	5.4	4.1	98 (15)
3	7.9	14.2	11.5	78 (12)
4	20.5	15.0	17.8	45 (7)
5	43.6	11.2	36.8	19 (3)
6	69.9	42.6	41.7	12 (2)

[a]*Only patients with a complete data set were included in the analysis of the accuracy of the scoring system. CTLS: clinical tumor lysis syndrome.*

Discussion

This study shows that TLS is a relatively common complication in patients with AML treated with intensive chemotherapy and receiving standard prophylactic measures such as hyperhydration and allopurinol. We divided TLS into CTLS and LTLS and found that only the development of CTLS implies higher induction mortality. The separate analysis of risk factors for CTLS and LTLS shows that impaired renal function, high WBC count and high serum levels of uric acid and LDH at presentation are the main risk factors for both forms of TLS. A simple scoring system was developed and validated for clinical use, with an excellent discrimination for both CTLS and LTLS.

There have been some attempts to establish a uniform definition and classification of TLS. In 1993, Hande and Garrow[6] divided TLS into LTLS and CTLS. However, this definition did not take into account those patients who already had abnormal laboratory values. To address this issue, Cairo and Bishop[19] modified this definition of LTLS to include those changes in serum levels above normal values, as well as >25% changes from baseline values occurring within 3 days before and 7 days after the start of chemotherapy. In the present study, we adapted the latter definition taking into consideration that: (i) creatinine serum levels should be a diagnostic criterion for LTLS, rather than CTLS; and (ii) the definition of CTLS should be based only on clinical criteria, including oliguria. For this reason, we considered oliguria and dialysis, as well as cardiac arrhythmia/sudden death and seizures, as criteria for CTLS.

As far as we know, this single center study is the largest series analyzing the incidence and risk factors for TLS in patients with AML. The incidence of CTLS was 5%, similar to that previously reported in patients with AML.[9,20] The incidence of CTLS in AML patients seems to be lower than that reported in patients with acute lymphoid leukemia (ALL) or high grade non-Hodgkin's lymphoma (NHL),[7,21-23] in whom it ranges from 11% to 25%.

Few studies have analyzed the incidence of LTLS in patients with AML. Razis *et al.*[24] reported that the incidence of LTLS was 57% among 41 patients with hyperleukocytic acute leukemia (WBC >100×10^9/L), which was comparable to the 45% found in our study (*data not shown*). In the study by Annemans *et al.*,[20] the incidence of hyperuricemia in 204 patients with AML was 14%, but the incidence of LTLS was not reported. In a recently published series of 194 patients with AML or advanced myelodysplastic syndrome,[8] the incidence of LTLS was 10%, lower than the 17% found in the present study. In any case, the global incidence of LTLS in AML seems to be far lower than the 42–66% reported in ALL and high-grade NHL.[5,6]

While spontaneous TLS is well described in patients with Burkitt's lymphoma,[21] it is thought to occur less commonly in AML. Most previous studies of AML considered TLS only after the start of chemotherapy, and none of them analyzed the incidence of spontaneous TLS. As a result, only a small number of cases of spontaneous TLS have been described in AML.[25-27] Interestingly, in our study cohort, 25% of the cases of TLS (eight cases with CTLS and 24 cases with LTLS) occurred before the initiation of chemotherapy.

The most common laboratory features of TLS were increased serum creatinine levels and hyperphosphatemia. Hyperuricemia was less common, occurring in 45% of the cases of TLS, probably because all patients received prophylaxis with allopurinol and this management was effective in some of them. It could be argued that at least some of the cases of renal failure in patients with TLS and normal serum levels of uric acid were due to the precipitation of calcium phosphate in renal tubules.[4]

We observed that the TLS-related morbidity and mortality in AML was tangible (5% and 2%, respectively). Moreover, the development of CTLS was significantly associated with a higher death rate during induction therapy, mostly due to hemorrhage, TLS or both. Conversely, the development of isolated LTLS was not associated with a higher mortality during induction. Furthermore, when compared with patients without TLS, those with isolated LTLS did not show a higher renal morbidity during the hospitalization for induction therapy. Therefore, it seems reasonable to implement prophylaxis for TLS using more effective drugs, such as rasburicase,[10] in patients at high risk of developing CTLS rather than LTLS.

This study shows that high pretreatment LDH and creatinine levels are associated with a high risk of CTLS and LTLS in patients with AML. This association between both parameters and the development of TLS has already been described in patients with AML,[8,9] as well as in patients with lymphoid malignancies.[6,11,12] We also found that WBC count and serum uric acid levels at presentation were significant independent predictors for CTLS and LTLS.

Remarkably, the independent risk factors for CTLS and LTLS were the same, but multivariate analysis showed a higher relative risk of LTLS for baseline serum uric acid >7.5 mg/dL and creatinine >1.4 mg/dL when compared with CTLS. This is logical because both risk factors are also laboratory criteria defining LTLS.

Univariate analysis showed that patients with hepatosplenomegaly or M4–M5 FAB subtypes had an increased risk of CTLS and LTLS. These associations were previously described in the study by Seftel *et al.*[9] Although male gender has been reported to be an independent risk factor for LTLS,[8] we did not find an association between this variable and the development of LTLS. On the other hand, univariate analysis showed that age >60 years was associated with a higher risk of CTLS and LTLS, but it was not an independent prognostic factor.

To our knowledge, only one scoring system for the prediction of TLS in patients with AML has been reported so far.[8] However, this model, based on pretreatment uric acid and serum LDH levels, was designed to predict only LTLS. The scoring system developed in the present study showed an excellent discrimination for CTLS, and

also for LTLS. Using cut-offs levels of 2 and 3 points, the model shows a high sensitivity (95% and 89%, respectively) and specificity (67% and 80%, respectively) for predicting CTLS.

The implication of such a discriminative capability of the model is that risk-adapted management of TLS would be possible in AML. This model could be useful for selecting high-risk patients for alternative prophylaxis, for instance with rasburicase. In fact, the guidelines on the management of AML from the British Committee for Standards in Haematology make an imprecise recommendation for the use of rasburicase with chemotherapy in patients with hyperleukocytosis at risk of TLS.[28] The proposed scoring system would allow a more precise and accurate selection of high-risk patients who should receive rasburicase.

In conclusion, TLS is a relatively common complication during induction therapy in patients with AML. Only one-third of patients with LTLS criteria finally developed CTLS, that is, the form of TLS in which a higher induction mortality rate is observed. Increased pretreatment WBC counts, serum creatinine, uric acid and LDH levels are the main risk factors for the development of CTLS and LTLS in patients with AML. We have developed and validated a simple, predictive scoring system for CTLS. This could be a useful tool for selecting high-risk patients who should receive alternative prophylaxis.

Authorship and Disclosures

PM and MS contributed to the conception and design of the study. PM, DM and GO collected and interpreted the data. PM, IL and GM performed the statistical analysis. All authors reviewed the manuscript and approved the final version to be published.

The authors reported no potential conflicts of interest.

References

1. Boccia RV, Longo DL, Lieber ML, Jaffe ES, Fisher RI. Multiple recurrences of acute tumor lysis syndrome in indolent non-Hodgkin's lymphoma. Cancer 1985; 56:2295-7.
2. Przepiorka D, Gonzales-Chambers R. Acute tumor lysis syndrome in a patient with chronic myelogenous leukemia in blast crisis: role of high dose ara-C. Bone Marrow Transplant 1990;6:281-2.
3. Zusman J, Brow DM, Nesbit MF. Hyperphosphatemia, hyperphosphaturia and hypocalcemia in acute lymphoblastic leukemia. N Engl J Med 1973;289:1335-40.
4. Wechsler DS, Kastan MB, Fivush BA. Resolution of nephrocalcinosis associated with tumor lysis syndrome. Pediatr Hematol Oncol 1994;11:115-8.
5. Kedar A, Grow W, Neiberger RE. Clinical versus laboratory tumor lysis syndrome in children with acute leukemia. Pediatr Hematol Oncol 1995;12:129-34.
6. Hande KR, Garrow GC. Acute tumor lysis syndrome in patients with high-grade non-Hodgkin's lymphoma. Am J Med 1993;94:133-9.
7. Atra A, Gerrard M, Hobson R, Imeson JD, Ashley S, Pinkerton CR. Improved cure rate in children with B-cell acute lymphoblastic leukaemia (BALL) and stage IV B-cell non-Hodgkin's lymphoma (B-NHL): results of the UKCCSG 9003 protocol. Br J Cancer 1998; 77:2281-5.
8. Mato AR, Riccio BE, Qin L, Heitjan DF, Carroll M, Loren A, et al. A predictive model for the detection of tumor lysis syndrome during AML induction therapy. Leuk Lymphoma 2006;47:877-83.
9. Seftel MD, Bruyere H, Copland M, Hogge DE, Horsman DE, Nantel SH, et al. Fulminant tumour lysis syndrome in acute myelogenous leukaemia with inv(16)(p13;q22). Eur J Haematol 2002; 69:193-9.
10. Goldman SC, Holcenberg JS, Finklestein JZ, Hutchinson R, Kreissman S, Leonard Johnson F, 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.
11. Wossmann W, Schrappe M, Meyer U, Zimmermann M, Reiter A. Incidence of tumor lysis syndrome in children with advanced stage Burkitt's lymphoma/leukemia before and after introduction of prophylactic use of urate oxidase. Ann Hematol 2003;82: 160-5.
12. Seidemann K, Meyer U, Jansen P, Yakisan E, Rieske K, Führer M, et al. Impaired renal function and tumor lysis syndrome in pediatric patients with non-Hodgkin lymphoma and B-ALL. Observations from the BFM trial. Klin Padiatr 1998;210:279-84.
13. Cheson BD, Cassileth PA, Head DR, Schiffer CA, Bennett JM, Bloomfield CD, et al. Report of the National Cancer Institute-sponsored workshop on definitions of diagnosis and response in acute myeloid leukemia. J Clin Oncol 1990;8:813-9.
14. Haviland MG. Yates's correction for continuity and the analysis of 2×2 contingency tables. Stat Med 1990; 9:363-7;discussion 369-83.
15. Cox DR. The analysis of binary data. London, UK: Metheun; 1970. p. 87-90.
16. Dixon WJ. BMDP Statistical Software. Berkeley, CA: University of California Press, 1990.
17. Hosmer DW, Lemeshow S. Applied Logistic Regression. New York: John Wiley. 1989.
18. Egan JP. Signal Detection Theory and ROC analysis. New York, NY: Academic Press. 1975.
19. Cairo MS, Bishop M. Tumor lysis syndrome: new therapeutic strategies and classification. Br J Haematol 2004; 127:3-11.
20. Annemans L, Moeremans K, Lamotte M, Garcia Conde J, Van Den Berg H, Myint H, 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.
21. Cohen LF, Balow JE, Magrath IT, Poplack DG, Ziegler JL. Acute tumor lysis syndrome. A review of 37 patients with Burkitt's lymphoma. Am J Med 1980;68:486-91.
22. Bowman WP, Shuster JJ, Cook B, Griffin T, Behm F, Pullen J, 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;14:1252-61.
23. Stapleton FB, Strother DR, Wyatt RJ, McKay CP, Murphy SB. Acute renal failure at onset of therapy for advanced stage Burkitt lymphoma and B cell acute lymphoblastic lymphoma. Pediatrics 1988;82:863-9.
24. Razis E, Arlin ZA, Ahmed T, Feldman EJ, Puccio C, Cook P, et al. Incidence and treatment of tumor lysis syndrome in patients with acute leukemia. Acta Haematol 1994;91: 171-4.
25. Duda J, Zoger S. Presentation of M4 acute myeloid leukemia in anuric renal failure with hyperuricemia and enlarged kidneys. J Pediatr Hematol Oncol 2002;24:55-8.
26. Lotfi M, Brandwein JM. Spontaneous acute tumor lysis syndrome in acute myeloid leukemia? A single case report with discussion of literature. Leuk Lymphoma; 29:625-8.
27. Riccio B, Mato A, Olson EM, Berns JS, Luger S. Spontaneous tumor lysis syndrome in acute myeloid leukemia: two cases and a review of the literature. Cancer Biol Ther 2006;5:1614-7.
28. Milligan D. W, Grimwade D, Cullis J. O, Bond L, Swirsky D, Craddock C, et al. Guidelines for the management of acute myeloid leukaemia in adults. Br J Hematol 2006;135:450-74.