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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

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Summary

In tumour lysis syndrome (TLS), metabolic alterations caused by the destruction of malignant cells manifest as laboratory abnormalities with (clinical TLS) or without (laboratory TLS) organ dysfunction. This prospective multicentre cohort study included 153 consecutive patients with malignancies at high risk for TLS (median age 54 years (interquartile range, 38–66). Underlying malignancies were acute leukaemia (58%), aggressive non-Hodgkin lymphoma (29.5%), and Burkitt leukaemia/lymphoma (12.5%). Laboratory TLS developed in 17 (11.1%) patients and clinical TLS with acute kidney injury (AKI) in 30 (19.6%) patients. After adjustment for confounders, admission phosphates level (odds ratio [OR] per mmol/l, 5.3; 95% confidence interval [95% CI], 1.5–18.3), lactic dehydrogenase (OR per x normal, 1.1; 95%CI, 1.005–1.25), and disseminated intravascular coagulation (OR, 4.1; 95%CI, 1.4–12.3) were associated with clinical TLS; and TLS was associated with day-90 mortality (OR, 2.45; 95%CI, 1.09–5.50; $P = 0.03$). In this study, TLS occurred in 30.7% of high-risk patients. One third of all patients experienced AKI, for which TLS was an independent risk factor. TLS was associated with increased mortality, indicating a need for interventional studies aimed at decreasing early TLS-related deaths in this setting.

Keywords: acute kidney failure, haematologic malignancy, intensive care units, haemodialysis, hyperphosphataemia.

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Tumour lysis syndrome (TLS) is a life-threatening complication of cancer treatment in patients with extensive, rapidly growing, chemosensitive malignancies. TLS results from the rapid destruction of malignant cells, which abruptly release intracellular ions, proteins, and metabolites into the extracellular space (Cairo & Bishop, 2004; Coiffier *et al*, 2008). The release of potassium, calcium, phosphates, and uric acid leads to a constellation of metabolic disturbances that can cause acute kidney injury (AKI), usually via uric-acid crystal deposition in the renal tubules. Another cause of AKI is calcium-phosphate deposition related to hyperphosphataemia. AKI may, in itself, cause substantial morbidity and mortality (Metnitz *et al*, 2002). In addition, AKI leads to further increases in the above-listed metabolites, most notably potassium and phosphates, which may cause cardiac arrhythmia or sudden death (Jeha, 2001; Davidson *et al*, 2004). Whereas uric acid deposition can be prevented by administering recombinant urate oxidase (rasburicase), severe hyperphosphataemia requires renal replacement therapy (RRT) to ensure rapid phosphates clearance (Cairo & Bishop, 2004; Coiffier *et al*, 2008).

Early recognition of patients at high-risk for TLS is mandatory to enable a risk-based strategy for the prevention of TLS and its adverse clinical consequences. TLS typically occurs in patients with aggressive haematological malignancies (acute leukaemia, Burkitt lymphoma, or other high-grade non-Hodgkin lymphoma [NHL]) (Flombaum, 2000; Jeha, 2001; Pui, 2001; Coiffier *et al*, 2008). In addition to the type of tumour and its sensitivity to chemotherapeutic agents, features related to the tumour burden (large tumour mass, lactate dehydrogenase [LDH] >1500 iu, and extensive bone marrow involvement) are known to influence the risk of TLS (Cohen *et al*, 1980).

TLS is believed to develop in 10% to 50% of patients with aggressive haematological malignancies (Annemans *et al*, 2003; Mato *et al*, 2006; Montesinos *et al*, 2008). AKI occurs in up to one-third of these patients (Mato *et al*, 2006; Montesinos *et al*, 2008). However, little is known regarding the current incidence of TLS in patients with aggressive haematological malignancies, as most studies were performed before the introduction of routine rasburicase therapy and without defining TLS based on uniform diagnostic criteria (Patte *et al*, 2002; Mato *et al*, 2006; Montesinos *et al*, 2008).

The primary objective of this study was to assess the prevalence of TLS in patients with aggressive haematological malignancies and high tumour burdens. The secondary objective was to assess risk factors for AKI and unfavourable outcomes in this setting.

Patients, study design and methods

This prospective multicentre study took place in 14 university-affiliated hospitals between 1 January 2010, and 30 June 2010. A dedicated haematology ward and a closed intensive

care unit (ICU) were available in each of the participating hospitals. The study was approved by our institutional review board, which waived the need for written informed consent. Patients and their next of kin were nevertheless informed about the study, and none refused to participate.

Consecutive adults (≥18 years) with aggressive haematological malignancies were included. We selected high-risk patients, defined as patients in whom an aggressive malignancy and high tumour burden indicated high probabilities of TLS and early death, based on published criteria (Coiffier *et al*, 2008). Aggressive malignancies were acute myeloid leukaemia (AML), acute lymphoblastic leukaemia (ALL), aggressive NHL (diffuse large B cell lymphoma, acquired immunodeficiency syndrome [AIDS]-related lymphoma, and Burkitt leukaemia/lymphoma). Large tumour burden was defined as a high leucocyte count ($>10 \times 10^9$/l) in promyelocytic AML, $>30 \times 10^9$/l in other AML, or $>100 \times 10^9$/l in ALL), bulky tumour (>7.5 cm), LDH higher than 1500 iu, or NHL Ann Harbor stage III or IV system. Burkitt leukaemia/lymphoma was always considered at high risk for TLS.

Data collection and definitions

Laboratory TLS and clinical TLS were defined on the basis of the daily recorded laboratory and clinical values based on Cairo-Bishop criteria (Cairo & Bishop, 2004) (Table I). AKI was defined according to the Acute Kidney Injury Network classification scheme (Mehta *et al*, 2007) as a serum creatinine increase ≥26.4 μmol/l or ≥150% from baseline or as urine output <0.5 ml/kg per h for 6 h or more. For patients whose baseline serum creatinine level was unknown, this variable was estimated using the Modification of Diet in Renal Disease formula assuming a normal glomerular filtration rate (GFR) of 75 ml/min per 1.73 m², as recommended by recent guidelines (Bellomo *et al*, 2004; Khwaja, 2012).

Table I. Definitions of laboratory and clinical tumour lysis syndrome (TLS) (Coiffier *et al*, 2008).

Laboratory TLS At least two of the following	
Serum calcium	<1.75 mmol/l or −25% from baseline
Serum potassium	6 mmol/l or +25% from baseline
Serum uric acid	476 μmol/l or +25% from baseline
Serum phosphates	1.45 mmol/l or +25% from baseline
Clinical TLS Laboratory TLS as defined above plus at least one of the following	
Any stage of acute kidney injury, defined as follows (Mehta *et al*, 2007)	
Stage 1: Increase in serum creatinine ≥26.4 μmol/l or ≥50% from baseline or urine output <0.5 ml/kg per h for more than 6 h	
Stage 2: Increase in serum creatinine ≥200% from baseline or urine output <0.5 ml/kg per h for more than 12 h	
Stage 3: Increase in serum creatinine ≥300% from baseline or urine output <0.3 ml/kg per h for 24 h or anuria for 12 h	
Cardiac arrhythmia or sudden death	
Seizure	

Event-free survival was defined as survival on day 90 with complete remission for acute leukaemia or partial remission without progression for Burkitt leukaemia/lymphoma or NHL.

The data reported in Table II were collected for each patient. Daily blood-test data (phosphates, calcium, potassium, urea, creatinine, uric acid, and LDH) were collected over the first 3 days. In addition, factors potentially associated with AKI, including exposure to nephrotoxic agents, were sought routinely.

The need for ICU admission or RRT during hospitalization was evaluated for each patient.

Statistical analysis

Results are reported as median (interquartile range, IQR) or number and percentage. Categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate, and continuous variables using the nonparametric Wilcoxon test or Mann-Whitney test. We performed logistic regression analyses to identify variables significantly associated with clinical TLS and AKI, as measured by the estimated odds ratio (OR) with the 95% confidence interval (95%CI). Variables yielding *P* values lower than 0.20 in the bivariate analyses were entered into backward stepwise logistic regression models where clinical TLS, and AKI were the variables of interest. The critical *P* value for removal was 0.1. Co-linearity and interactions were tested. The Hosmer-Lemeshow test was used to check goodness-of-fit. Given the number of events, a maximum of four, three, and four variables was allowed in the models testing associations with clinical TLS, and AKI, respectively. Last, we forced variables suspected to be associated with outcome into the final models.

To address factors independently associated with outcome, we performed a Conditional Cox model to identify variables significantly associated with mortality, as measured by the estimated OR with 95%CI. Variables yielding *P* values lower than 0.20 in the bivariate analyses were entered into a backward conditional Cox model where mortality was the variable of interest. The critical *P* value for removal was 0.1. Each patient was followed at least until day 90. Last, in order to validate this model, clinically relevant variables were forced in the final model.

A clinical TLS risk assessment score was then computed using odds of variables independently associated with clinical TLS. Four risk class were defined: low risk, defined as a risk score associated with a high sensitivity; intermediate, defined as the score lower than the optimal cut-off value and two classes (high and very high risk), defined by a high specificity. The receiver-operating characteristic (ROC) curves of the proportion of true positives against the proportion of false positives was then plotted, depending on the prediction rule used to classify patients as having clinical TLS. Finally, highly

Table II. Characteristics of patients without tumour lysis syndrome (TLS), with laboratory TLS, and with clinical TLS.

	No TLS $N = 106$ (69.3%)	Laboratory TLS $N = 17$ (11.1%)	Clinical TLS $N = 30$ (19.6%)	P value*
Male gender	58 (55)	10 (59%)	20 (67)	0.49
Age (years)	54 (37–67)	45 (30–63)	58 (47–66)	0.44
Baseline plasma creatinine (μmol/l)	77 (60–88)	80 (70–88)	79 (70–88)	0.42
Chronic cardiac dysfunction	2 (2)	2 (12)	1 (3)	0.11
Past history of hypertension	21 (20)	4 (24)	12 (40)	0.08
Chronic respiratory insufficiency	2 (2)	1 (6)	4 (13)	0.03
Diabetes	11 (10)	2 (12)	2 (7)	0.39
HIV infection	8 (8)	1 (6)	3 (10)	0.96
Underlying malignancy				
Acute leukaemia	59 (56)	12 (71)	18 (60)	0.53
Including AML	53	9	15	
Including ALL	6	3	3	
NHL	34 (32)	2 (12)	9 (30)	
Including B-cell NHL	31	1	8	
Including T-cell NHL	3	1	1	
Burkitt lymphoma/leukaemia	13 (12)	3 (18)	3 (10)	
Non haematopoietic malignant infiltration	37 (35)	6 (35)	11 (37)	0.98
Factors associated with AKI				
Contrast medium	3 (3)	1 (6)	2 (7)	0.56
ACEI/ARA	9 (8)	1 (6)	1 (3)	0.63
Aminoglycosides	4 (4)	1 (6)	6 (20)	**0.008**
Glycopeptides	9 (8)	0	2 (7)	0.44

HIV, human immunodeficiency virus; AML, acute myeloid leukaemia; ALL, acute lymphocytic leukaemia; NHL, non-Hodgkin lymphoma; AKI, acute kidney injury; ACEI, angiotensin-converting enzyme inhibitors; AAR, angiotensin II receptor antagonists.
*P values are reported for comparisons across the three patient groups (no TLS, laboratory TLS, clinical TLS).
Bold values in tables are variables with P values < 0.05.

sensitive value, optimal cut-off value (defined as threshold values that maximized the sum of sensitivity and specificity) and highly specific value were determined on the ROC curves.

All tests were two-sided, and P values lower than 0.05 were considered statistically significant. Statistical tests were done using the SPSS 13 software package (IBM, Armonk, NY, USA).

Results

Study population

One hundred and fifty-three patients with newly diagnosed haematological malignancies considered at high risk for TLS were included. Tables II and III list their main characteristics.

Cancer chemotherapy was started on the admission day in most patients ($n = 133$; 86.9%) and on the next day in the remaining patients. The most common chemotherapy regimens were cytosine arabinoside and anthracycline ($n = 72$, 47.1%) and COP (cyclophosphamide, vincristine, prednisolone)-derived regimens ($n = 56$, 36.6%). Rituximab was given in combination with cancer chemotherapy in 21 (13.7%) patients. Most patients received standard chemotherapy regimens ($n = 132$; 86.3%); of the remaining 21 patients, 7 (7/153, 4.6%) received reduced-dose regimens and 14 (14/153, 9.2%) full-dose regimens with modified administration schedules.

Characteristics of tumour lysis syndrome and prevalence of AKI

Of the 153 patients, 47 (30.7%) had TLS including 17 (11.1%) with laboratory TLS and 30 patients (19.6%) with clinical TLS (Fig 1). All patients in the clinical TLS group had AKI (including 12 patients, six patients and 12 patients with stage 1, 2 and 3 AKI respectively); in addition, four patients had seizures due to TLS-related hypocalcaemia. None experienced sudden death or cardiac arrhythmia. Tables II and III report the clinical and laboratory characteristics at admission. The TLS rate showed no significant differences across haematological malignancies (Table II).

The treatment of TLS always included hydration, with a median fluid volume of 3000 ml per day (range, 2000–4000). In addition, 20 (13.1%) patients received bicarbonates on day 1. At admission, rasburicase was given to 80 (52.3%) patients, allopurinol to 54 (35.3%) patients, and both to 19 (12.4%) patients. In the rasburicase-treated patients, the median dosage was 0.17 (0.11–0.20) mg/kg. Tables S1 and S2

Table III. Laboratory abnormalities, treatment, and outcome of patients without tumour lysis syndrome (TLS), with laboratory TLS, and with clinical TLS.

	No TLS *N* = 106 (69.3%)	Laboratory TLS *N* = 17 (11.1%)	Clinical TLS *N* = 30 (19.6%)	*P* value*
Laboratory findings at admission				
Phosphates (mmol/l) at admission	1.17 (0.96–1.36)	1.20 (0.90–1.80)	1.56 (1.13–1.80)	**0.002**
Calcium (mmol/l) at admission	2.20 (2.10–2.30)	2.20 (2.00–2.40)	2.20 (1.99–2.60)	0.93
Urate (μmol/l) at admission	212 (105–328)	315 (180–519)	532 (129–799)	**0.0003**
Potassium (mmol/l) at admission	3.8 (3.4–4.1)	4.0 (3.7–4.6)	4.1 (3.3–4.9)	0.20
LDH (×normal) at admission	2.6 (1.5–4)	4.7 (3.5–7.5)	5.0 (3.0–11.0)	**<0.0001**
Plasma creatinine (μmol/l)	71 (56–90)	78 (55–89)	153 (93–189)	**<0.0001**
Diuresis (l/day)	2.5 (1.8–3.9)	3.0 (2.1–4.0)	1.3 (0.9–2.4)	**0.0003**
DIC at admission	26 (25)	5 (29)	18 (60)	**0.002**
Treatments on day 1				
Hydration (l)	3 (2–4)	4 (3.8–5)	4 (3–5)	**0.001**
Bicarbonates	13 (12)	3 (18)	4 (13)	0.83
Rasburicase	48 (45)	12 (71)	20 (67)	**0.04**
Allopurinol	40 (38)	4 (24)	10 (33)	0.49
Diuretics	27 (25)	8 (47)	9 (30)	0.22
ICU admission	38 (36)	7 (41)	21 (70)	**0.004**
Need for RRT	10 (9)	1 (6)	16 (53)	**<0.001**
Remission†	79 (75)	11 (65)	21 (72)	0.64
90-day mortality†	21 (20)	7 (41)	9 (31)	0.11

TLS, tumour lysis syndrome; LDH, serum lactic dehydrogenase; DIC, disseminated intravascular coagulation; ICU, intensive care unit; RRT, renal replacement therapy.

**P* values are reported for comparisons across the three patient groups (no TLS, laboratory TLS, clinical TLS).

†Vital status and remission on day 90 was known for 151 of the 153 patients; the remaining two patients were lost to follow-up.

Bold values in tables are variables with *P* values < 0.05.

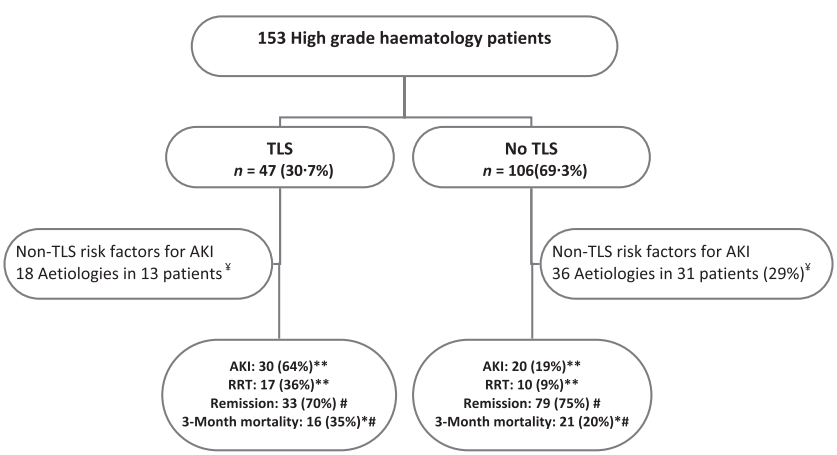

Fig 1. Flowchart of patients included in the study according to the presence of TLS. TLS, tumour lysis syndrome; AKI, acute kidney injury; RRT, renal replacement therapy; CR, complete remission.

¥ *P* = 0·99 between TLS and non-TLS groups
* *P* = 0·052 between TLS and non-TLS groups
** *P*<0·01 between TLS and non-TLS groups
# 151 patients were evaluated at day-90. The two remaining patients were lost for follow-up

in Appendix S1 shows the changes in uric acid levels over the first 3 days. Figures S1, S2 and S3 in Appendix S1 shows the changes in serum phosphates, calcium, and creatinine levels over the first 3 days. Overall, 66 patients (43.1%) required ICU admission, including 21 patients with clinical TLS (70%). Of the 66 patients admitted to the ICU, 27 required RRT (17.6% of the overall population), including 17 with TLS (36%; of whom 16 had clinical TLS). The main reasons for ICU admission were monitoring in 19 patients (29% of ICU admission), RRT as consequences of TLS in 17 patients (26%), acute respiratory failure in 15 patients (23%) and sepsis or septic shock in 10 patients (15%). The five remaining patients were admitted as consequences of coma (n = 3), leucostasis (n = 1) or a non-TLS related AKI (n = 1).

Compared to patients without TLS, patients with TLS (either clinical or laboratory) had higher LDH levels at admission (5.0 × normal [3.0–9.0] vs. 2.6 × normal [1.5–4.0], $P < 0.0001$) and received larger fluid volumes (4000 ml [3000–5000] vs. 3000 ml [2000–4000], $P = 0.04$). A higher proportion of patients with TLS (either clinical or laboratory) received rasburicase on day 1 (32 [68%] vs. 48 [45%], $P = 0.01$).

Risk factors for clinical tumour lysis syndrome and acute kidney injury

Prevalence of AKI was 32.7% ($n = 50$). Overall, despite similar rate of non-TLS related risk factors of AKI, prevalence of AKI in patients with and without TLS was of 63.8% ($n = 30$) and 18.9% ($n = 20$) respectively ($P < 0.0001$; Fig 1). Prevalence of TLS was 18.5% in patients without risk factors for AKI or TLS ($n = 81$), 40.6% in patients with TLS or any other risk factors ($n = 59$) and 84.6% in patients with both TLS and an additional risk factor for AKI ($n = 13$) ($P < 0.0001$; Fig 2). Overall, 27 patients required RRT (17.6%) including 10 patients without TLS (9%) and 17 patients with TLS (36%) ($P < 0.0001$; Fig 1).

Only three variables were independently associated with clinical TLS when entered into a conditional logistic regression model: serum phosphates level (OR per mmol/l, 5.3; 95%CI, 1.5–18.3), tumour burden as assessed by LDH (OR per x normal, 1.1; 95%CI, 1.005–1.25), and disseminated intravascular coagulation (OR, 4.1; 95%CI, 1.4–12.3). The model was well calibrated. When forced into the model, the underlying haematological malignancy, rasburicase use, and hydration on day 1 were not selected and did not change the results. A clinical TLS risk assessment score was then developed according to the result of this multivariate analysis (Table IV). This score ranged from 0 to 20 and its performance to detect clinical TLS was fair [area under ROC curve 0.78 (95%CI, 0.68–0.87)]. Four risk classes were defined (from low risk to very high risk) and prevalence of clinical TLS increased steadily from 6 to 67% across these classes (Table V).

Only two variables were independently associated with AKI when entered into a conditional logistic regression model: laboratory TLS (OR, 4.5; 95%CI, 1.8–11.1) and disseminated intravascular coagulation at admission (OR, 3.5; 95%CI, 1.5–7.9). The model was well calibrated. When forced into the model, the underlying haematological malignancy and other risk factors for AKI (including use of aminoglycosides) were not selected and did not change the results.

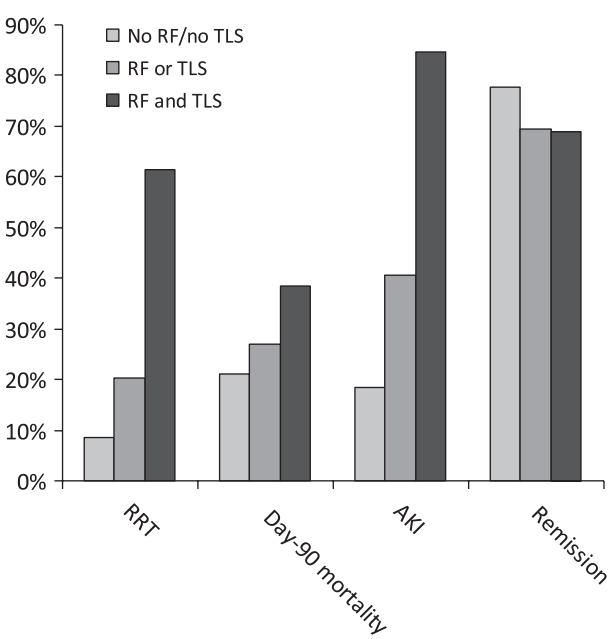

Fig 2. Rate of renal replacement therapy (RRT), day-90 mortality, acute kidney injury (AKI) and partial or complete remission in patients without risk factors (RF) of AKI ($n = 81$), in patients with TLS or any other risk factor for AKI ($n = 59$) and in patients with both TLS and other risk factors for AKI ($n = 13$); ($P < 0.0001$, $P = 0.35$, $P < 0.0001$ and $P = 0.51$ respectively). Vital status and remission on day 90 was known for 151 of the 153 patients; the remaining two patients were lost to follow-up.

Influence of tumour lysis syndrome on day-90 mortality and day-90 event-free survival

In all, 37 (24.5%) patients died by day 90; for two patients with clinical TLS, vital status on day 90 was unknown. Patients without TLS had a trend toward lower day-90 mortality (20% vs. 35% in patients with TLS, $P = 0.052$). The

Table IV. Clinical TLS risk assessment score.

	Points
Lactate dehydrogenase (per 10 × normal)*	1
Phosphates (per mmol/l)†	5
DIC at admission	4

DIC, disseminated intravascular coagulation.
*If lactate dehydrogenase <10 × N then 0.
†Each mmol of phosphates, entered as a whole number add 5 points. If phosphates <1 mmol then 0.

Table V. Clinical TLS risk assessment score risk classes and prevalence of TLS.

	Score	*n*	Clinical TLS prevalence (%)	Need for RRT (%)
Low risk	≤5	72	6	4
Intermediate risk	6–9	40	20	15
High risk	10–13	29	53	38
Very high risk	≥14	12	67	58

TLS, tumour lysis syndrome; RRT, renal replacement therapy.

main causes of death within the first 90 days were uncontrolled malignancy ($n = 23$), shock or severe sepsis ($n = 9$), uncontrolled TLS ($n = 4$), and anthracycline toxicity ($n = 1$).

When entered in a Cox model where mortality was the variable of interest, TLS (either clinical or laboratory) (OR, 1.92; 95%CI, 1.03–3.66, $P = 0.04$) and human immunodeficiency virus infection (OR, 2.54; 95%CI, 1.06–6.1, $P = 0.04$) were independently associated with outcome. When forced into the model, the underlying haematological malignancy, age, and male gender were not selected and did not change the results.

Overall, of the 151 patients that could be evaluated at day 90, 109 patients (72.2%) survived and achieved partial or complete remission at day 90, including 75 patients without TLS (71.4%) and 34 patients with TLS (73.9%).

Discussion

To our knowledge, this is the largest study specifically designed to evaluate the incidence and clinical consequences of TLS in the rasburicase era in patients with aggressive haematological malignancies and high tumour burdens. One-third of patients experienced TLS. In addition, despite the availability of rasburicase, TLS remained the main factor leading to AKI in these patients and clinical TLS was associated with increased mortality. Our study strongly supports an aggressive strategy combining early TLS diagnosis and effective prevention to limit the adverse consequences of TLS in this subset of patients.

TLS is a well-known complication of high-grade haematological malignancies, most notably aggressive NHL, AML, and ALL (Cohen *et al*, 1980; Flombaum, 2000; Jeha, 2001; Coiffier *et al*, 2008), and has been reported in 10–50% of adults with such malignancies (Patte *et al*, 2002; Annemans *et al*, 2003; Mato *et al*, 2006; Montesinos *et al*, 2008). Despite the high incidence and severe prognosis of TLS, few outcome studies have been conducted, and most of the available data come from retrospective case series (Boles *et al*, 1984; Annemans *et al*, 2003; Mato *et al*, 2006; Montesinos *et al*, 2008). In addition, until recently, no universally recognized definition of TLS was available (Cairo & Bishop, 2004; Coiffier *et al*, 2008). The largest study to date in patients with AML showed a 17% incidence of TLS (Montesinos *et al*, 2008). However, this study was done in a single centre, before the advent of rasburicase, and did not select patients with high tumour burden (Montesinos *et al*, 2008). A previous study suggested that urate-oxidase therapy may dramatically reduce the TLS rate in patients with aggressive haematological malignancies (Patte *et al*, 2002). However, it was performed in paediatric patients and before the development of universally accepted definitions of AKI and TLS (Patte *et al*, 2002). Last, although several studies evaluated the benefit of urate-oxidase therapy to reduce urate level in healthy subject or patients with haematological malignancy, most of these were retrospective and failed to concomitantly evaluate the prevalence of TLS (Mahmoud *et al*, 1998; Coiffier *et al*, 2003; Wang *et al*, 2006; Campara *et al*, 2009). Our study was specifically designed to evaluate the incidence of TLS in patients with tumours at high risk for TLS. In this population, 30.7% of patients experienced TLS and two-thirds of patients with TLS had clinical manifestations of the syndrome. As previously described, AKI was the main clinical manifestation of TLS (Montesinos *et al*, 2008).

The most striking finding from our study is the adverse impact of TLS on outcomes. First, despite similar rates of non-TLS related AKI risk factors, TLS was the only risk factor independently associated with AKI in this study. In addition, our study suggests that clinical TLS may be associated with a higher mortality rate. Previous studies suggested that AKI complicating TLS increased the likelihood of death, with mortality rate ranging from 2 to 20% (Darmon *et al*, 2007, 2010; Montesinos *et al*, 2008). Although, the day 90 mortality in this study may seem to be high, it probably reflects the severity of the underlying malignancy and is consistent with the mortality of patients with aggressive haematological malignancies (Milpied *et al*, 2004; Tallman *et al*, 2004; Galicier *et al*, 2007; Todeschini *et al*, 2012). AKI has also been demonstrated to decrease the complete remission rate in cancer patients (Munker *et al*, 1998). These findings are not surprising. The morbidity and mortality associated with AKI have remained unchanged over the last decades (Metnitz *et al*, 2002; Palevsky *et al*, 2008). Several studies suggest that AKI *per se*, independently of the nature or severity of the underlying disease and from the metabolic consequences of renal failure, may influence the chances of survival (Levy *et al*, 1996; Metnitz *et al*, 2002; Chertow *et al*, 2005). In addition, several studies underlined the prognostic impact of serum creatinine elevation (Chertow *et al*, 2005; Loef *et al*, 2005). These studies suggest that AKI may be capable of inducing or worsening dysfunctions of other organs (Li *et al*, 2009). Interestingly, in the rasburicase era, the serum phosphate concentration seems to be the main risk factor associated with clinical TLS, i.e., with AKI. In our study, a 1-mmol increase in serum phosphates was associated with a 5-fold increase in the risk of clinical TLS. To help physicians assess the risk of clinical TLS in patients with aggressive haematological malignancies, we computed a risk model of clinical TLS. Although performance of this score was fair in this study, validation of this score on a prospective and independent cohort is mandatory. Our results underline clinical consequences of TLS and its prognostic impact, suggesting that early TLS detection is required in order to implement adequate preventive strategies aimed at preventing renal injury or further renal impairment.

Our study has several limitations. First, we focused on patients with aggressive haematological malignancies and high tumour burdens. Therefore, our results are not relevant to patients with low-grade haematological malignancies or with aggressive haematological malignancies but limited tumour burdens. In addition, our study focused on TLS

occurring within 3 days after the diagnosis of the haematological malignancy. This point may explain the high incidence of clinical TLS at study inclusion. Our results suggest that laboratory TLS may have occurred before the diagnosis of the haematological malignancy and, therefore, before study inclusion. Thus, as indicated in a previous study, TLS may occur spontaneously in patients with malignancies at high risk for TLS (Darmon *et al*, 2010). In addition, optimal TLS prevention was not used routinely in our patients. Thus, half the included patients did not receive rasburicase on the day of inclusion, and 13% received bicarbonates, which may increase the risk of calcium-phosphate crystals deposition. Better compliance with clinical guidelines might have diminished the rates of both laboratory and clinical TLS. However, our multicentre study provides an accurate snapshot of current practices regarding TLS prevention and treatment. The 90-day mortality rate was low in our study, and consequently we had limited statistical power for detecting specific effects of laboratory TLS and clinical TLS on day-90 mortality. However, we found a trend toward a higher crude mortality rate in the patients with TLS, as well as an independent association between TLS and day-90 mortality. Although further studies are needed to confirm our results, these suggest that TLS may influence long-term outcomes in patients with aggressive malignancies and high tumour burdens. Finally, as in several studies focusing on AKI, many patients presented with AKI without a reliable baseline serum creatinine on record. Baseline serum creatinine was therefore back calculated using the Modification of Diet in Renal Disease Study equation and assuming that the baseline estimated GFR is 75 ml/min per 1.73 m^2 as recommended (Bellomo *et al*, 2004; Khwaja, 2012). This method, although validated, may however misclassify several patients and this limit needs to be taken into account when interpreting our results (Závada *et al*, 2010).

In summary, our study clarifies the incidence of laboratory and clinical TLS in patients with haematological malignancies at high risk for TLS. Of these patients, one-third experienced laboratory TLS and one-fifth had clinical TLS. Our study confirms that TLS is an independent risk factor for AKI in this population and suggests an association with day-90 mortality. Additional studies are needed to assess comprehensive risk-based strategies, including aggressive fluid administration, avoidance of bicarbonates, routine rasburicase therapy, and early ICU admission of patients with clinical TLS or persistent hyperphosphataemia despite treatment, with the goal of decreasing the risk of progression from laboratory to clinical TLS. Until such studies are available, physicians must maintain a high degree of suspicion for TLS and must routinely implement preventive measures.

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Author contributions

M. Darmon, Francois Vincent, Laurent Camous, Emmanuel Canet, and Elie Azoulay designed the research study. Caroline Bonmati, Thorsten Braun, Denis Caillot, Jérome Cornillon, Sophie Dimicoli, Anne Etienne, Lionel Galicier, Alice Garnier, Stéphane Girault, Mathilde Hunault-Berger, Jean-Pierre Marolleau, Philippe Moreau, Emmanuel Raffoux, Christian Recher, Anne Thiebaud, Catherine Thieblemont were involved in data acquisition. M. Darmon, Francois Vincent, and Elie Azoulay analysed the study results. M. Darmon, Francois Vincent, Laurent Camous, and Elie Azoulay wrote the manuscript. All authors were involved in results interpretation and critical revisions of the final manuscript. All authors approved the final manuscript.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Urates levels according to TLS (median [IQR]).

Table S2. Urates levels according to Rasburicase use from day 1 to day 3.

Fig S1. Changes in serum levels of nonionized calcium over the first 3 days after study inclusion in patients without tumor lysis syndrome (TLS), with laboratory TLS, and with clinical TLS. The data are mean ± 95% confidence interval.

Fig S2. Changes in serum levels of nonionized phosphate over the first 3 days after study inclusion in patients without tumor lysis syndrome (TLS), with laboratory TLS, and with clinical TLS. The data are mean ± 95% confidence interval.

Fig S3. Changes in serum levels of nonionized creatinine (S3) over the first 3 days after study inclusion in patients without tumor lysis syndrome (TLS), with laboratory TLS, and with clinical TLS. The data are mean ± 95% confidence interval.

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