

Development of a predictive model for tumour lysis syndrome in patients with acute myeloid leukemia

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Tumor lysis syndrome (TLS) can be a life threatening complication during induction chemotherapy in patients with acute myeloid leukemia (AML). TLS is characterized by hyperuricemia, hyperkalemia, hyperphosphatemia, hypocalcemia and acute renal failure. These abnormalities may occur at presentation of AML due to increased catabolism and turn over of leukemic cells, 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.¹ Standard management of TLS includes generous hyperhydration, urine alkalinization and uric acid reduction with allopurinol to prevent urate nephropathy, and dialysis when acute renal failure can not be managed so far. In spite of these measures, TLS-related morbidity and mortality still occur in a sizeable proportion of patients with acute myeloid leukemia. In 2001, a randomized study performed in patients with lymphoma or leukemia demonstrated more rapid control and lower levels of plasma uric acid in those who received rasburicase compared to allopurinol.² Although recombinant urate oxidase is a safe drug more effective than allopurinol, its use may be cost-effective only for patients at risk of developing TLS. Then, efforts to define the population at risk of TLS among acute myeloid leukemia patients should be done.

We performed a single-centre retrospective chart review study aiming to: 1) Analyze incidence and outcome of TLS in patients with AML managed with hyperhydration and allopurinol, 2) Identify prognostic factors of TLS, and 3) Develop a predictive model to design a risk-adapted strategy for prophylaxis and therapy of TLS with urate oxidase.

Patients and Methods

Between January 1980 and December 2000, 614 consecutive adult patients were

diagnosed of *de novo* AML and started intensive chemotherapy in a single institution. Median age of the cohort was 53 years (range: 14–80). Biochemistry and blood count tests were performed at diagnosis and every 1–3 days during induction. Chemotherapy was based on combination of anthracycline with cytarabine with or without an additional drug. Prophylaxis of TLS consisted of intravenous hydration (>2 L/day) and oral allopurinol.

For the present study we adapted Cairo-Bishop definition and gradation of TLS.³ LTLS was defined as either a 25% change from baseline or level above or below laboratory normal values (ULN) ($K^+ > 5$ mEq/L, Uric Acid >7.5 mg/dL, Phosphate >5mEq/L, $Ca^{2+} < 8$ mEq/L) for any two or more of this parameters; or creatinine levels above ULN (>1.4 mg/dL) and level above ULN of at least one of the previously defined parameters. These criteria must be met within 3 days before and 7 days after the initiation of chemotherapy in absence of any other recognizable cause. CTLS was defined as the presence of LTLS and at least one of the following clinical complications: oliguric renal failure (<900 mL/day), hemodialysis, electrocardiographic signs of hyperkalemia or hypocalcemia in EKG, cardiac arrhythmia/sudden death, tetania, or seizures (Table 1).

Results

Overall, 101 patients (17%) developed TLS, 72 of them LTLS (12%). Incidence of CTLS was 5%, similar to previous studies in patients with leukemia or aggressive lymphoma (Table 2). Interestingly, Razis⁴ reported in a series of 41 patients with hyperleukocytic acute leukemia ($> 100 \times 10^9/L$) an incidence of TLS of 57%, comparable to 55% found in our study.

Clinical characteristics of CTLS and LTLS

Median day of onset of TLS was +2 (range -3 to +7). TLS occurred before chemotherapy (since day -3 until day 0) in 25 patients

Table 1. Definition and gradation of TLS.

| LTLS (A) (at least two 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 meq/L or 25% increase from baseline |
| Calcium | < 8 meq/L or 25% decrease from baseline |
| LTLS (B) | |
| Creatinine > 1,4 mg/dL and at least one | Uric Acid > 7.5 mg/dL, Potassium > 5 meq/L, Phosphorous > 5 meq/L, Calcium < 8 meq/L |
| CTLS | |
| LTLS (A) or (B), and at least one complication | Oliguria (<900 mL/day), Dialysis, Cardiac arrhythmia / sudden death, Electrocardiographic signs of hyperpotassemia or hypocalcemia, Seizures or tetania |

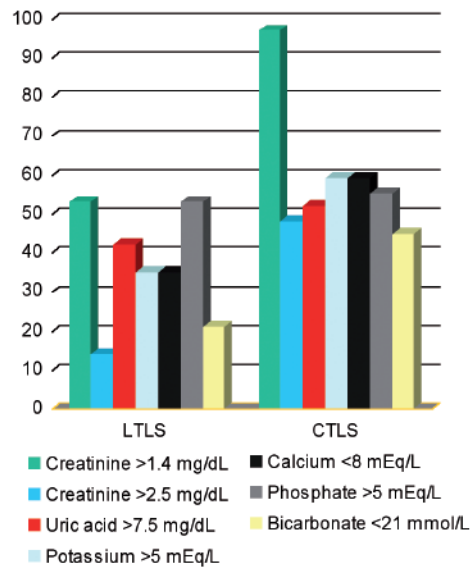


Figure 1. Frequency of laboratory abnormalities in LTLS and CTLS (since day -3 to TLS resolution).

Table 2. Reported LTLS and CTLS incidence in patients with acute leukemia and lymphoma.

| | Patient characteristics | Number of patients | LTLS (%) | CTLS (%) |
|---------------------------------|---|--------------------|----------|----------|
| Hande-Garrow, 1993 ⁵ | High grade lymphoma and high risk acute leukemia (WBC >25×10 ⁹ /L) | 102 | 42 | 6 |
| Razis, 1994 | Hyperleukocytic acute leukemia (WBC >100×10 ⁹ /L) | 41 | 57 | - |
| Kedar, 1995 ⁶ | Children with acute leukemia | 30 | 66 | 5 |
| Annemans, 2003 ⁷ | Non-Hodgkin lymphoma and acute leukemia | 722 | - | 3 |
| Mato, 2004 ⁸ | Adults with AML | 194 | 10 | - |
| Present study | Adults with <i>de novo</i> AML | 614 | 12 | 5 |

(25%), and it was induced by chemotherapy in 76 (75%). Laboratory abnormalities that occurred since day -3 to resolution of TLS are presented in Figure 1. Interestingly, all laboratory parameters were more frequently altered in CTLS than in LTLS.

Oliguria was the main clinical complication defining CTLS, occurring in 86% of cases. Other complications were dialysis (17%), arrhythmia/sudden death (14%), seizures/convulsions (10%), and electrocardiographic signs of hyperkalemia (3%) (Figure 2).

Outcome of CTLS and LTLS

Development of LTLS had no impact on induction death rate (21% vs 24%, *p*=0.51), but CTLS was associated with higher induction death rate (83% vs 24%, *p*<0.001). The main causes of death in patients with CTLS were hemorrhage and renal failure. In 14 patients (2%) CTLS was considered a major cause of death, due

to renal failure, arrhythmia/sudden death, or coma/convulsions (Figure 3).

Prognostic factors for CTLS

Univariate analysis showed that CTLS was significantly associated with FAB M4–M5, hepatomegaly, splenomegaly, GOT >50 UI/l, Creatinine >1.4 mg/dL, Uric acid >7.5 mg/dL, WBC >25×10⁹/L, and LDH >1 x ULN (Table 3).

Multivariate analysis was performed using categorized variables according to the most significant cut point obtained in univariate analysis. Pretreatment creatinine, WBC, uric acid and LDH were the factors with independent prognostic value for CTLS and LTLS (Table 4).

Predictive model for CTLS

According to the multivariate analysis, a prognostic

Table 3. Prognostic factors for TLS.

| Characteristic | CTLS n (%) | p value | LTLS n (%) | p value |
|----------------------------|---------------|---------|---------------|---------|
| Overall | 29/614 (5) | | 72/585 (12) | |
| Age (years) | | 0.3 | | 0.04 |
| ≤60 | 16 (4) | | 40 (10) | |
| >60 | 13 (6) | | 32 (16) | |
| Gender | | 0.19 | | 1 |
| Male | 21 (6) | | 42 (12) | |
| Female | 8 (3) | | 30 (12) | |
| WBC (×10 ⁹ /L) | | <0.001 | | <0.001 |
| ≤25 | 5 (1) | | 13 (3) | |
| 25-75 | 8 (7) | | 25 (23) | |
| >75 | 16 (15) | | 34 (28) | |
| LDH (xULN) (n=545) | | <0.001 | | <0.001 |
| ≤1 | 1 (1) | | 4 (2) | |
| 1-4 | 13 (4) | | 46 (16) | |
| > 4 | 13 (20) | | 17 (33) | |
| Creatinine (mg/dL) (n=605) | | <0.001 | | <0.001 |
| ≤1.4 | 16 (3) | | 47 (9) | |
| > 1.4 | 12 (24) | | 25 (68) | |
| Uric Acid (mg/dL) (n=583) | | <0.001 | | <0.001 |
| ≤7.5 | 15 (3) | | 47 (9) | |
| > 7.5 | 13 (23) | | 24 (54) | |
| FAB subtype | | 0.04 | | <0.001 |
| M4-M5 | 16 (8) | | 37 (23) | |
| Other | 13 (4) | | 35 (8) | |
| Hepatosplenomegaly | | <0.001 | | <0.001 |
| No | 8 (2) | | 42 (9) | |
| Yes | 21 (13) | | 30 (22) | |
| GOT (UI/l) (n=602) | | 0.01 | | 0.16 |
| ≤50 | 19 (4) | | 60 (11) | |
| > 50 | 8 (11) | | 12 (19) | |

Table 4. Multivariate analysis for prognostic factors of LTLS and CTLS.

| Prognostic factor | CTLS | | LTLS | |
|-------------------|---------|---------|---------|---------|
| | Exp (B) | P value | Exp (B) | P value |
| LDH | 2.06 | <0.001 | 1.6 | 0.009 |
| Uric Acid | 1.52 | <0.001 | 1.8 | <0.001 |
| Creatinine | 1.56 | 0.005 | 2.32 | <0.001 |
| WBC | 1.47 | 0.031 | 2.06 | <0.001 |

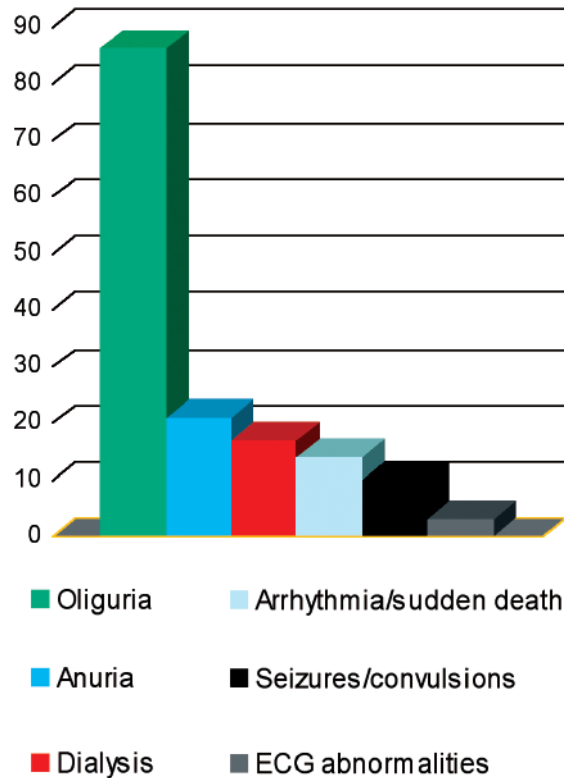


Figure 2. Clinical complications of CTLS.

Table 5. Scoring system of the predictive model for CTLS.

| Prognostic Factor | |
|-------------------|--|
| 1 point | WBC >25 and £75 LDH >1 and £4 |
| 3 points | WBC >75 LDH >4 Uric Acid >7.5 Creatinine >1.4 |

Table 6. Accuracy of the predictive model in the study population.

| SCORE (points) | CTLS n (%) | Patients n (%) | LTLS n (%) | Patients n (%) |
|----------------|---------------|-------------------|---------------|-------------------|
| 0-1 | 1 (0.3) | 306 (59) | 4 (1.3) | 305 (61) |
| 2-3 | 2 (2.5) | 81 (15) | 15 (19) | 79 (16) |
| 4-5 | 7 (9.6) | 73 (14) | 17 (26) | 66 (13) |
| ≥ 6 | 16 (25) | 64 (12) | 30 (62) | 48 (10) |
| All Patients | 26 (5) | 524 (100) | 66 (12) | 498 (100) |

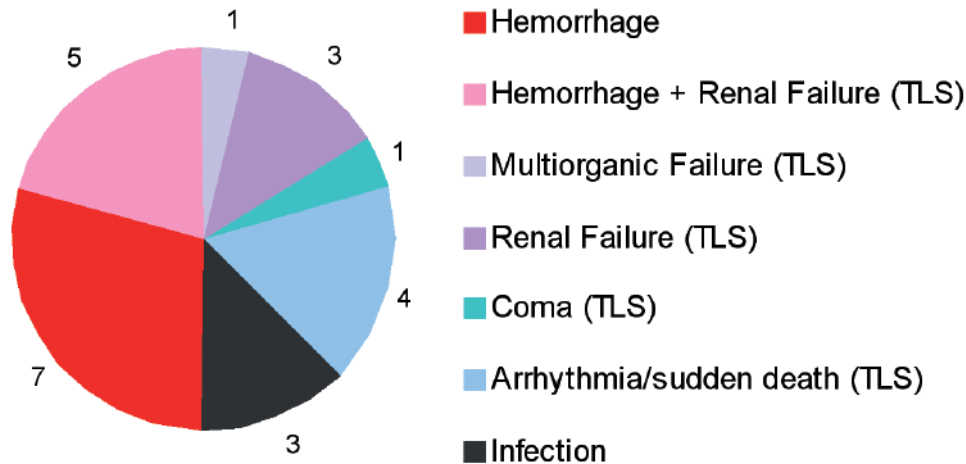


Figure 3. Causes of induction death in patients with CTLS (n= 24, 86%).

score system for CTLS was built assigning 3 points for creatinine >1.4 mg/dl, uric acid >7.5 mg/dL, WBC >75 ×10⁹/L, or LDH >4 × ULN; and 1 point for WBC >25 and ≤75 ×10⁹/L, or LDH >1 and ≤4 × ULN (Table 5). CTLS incidence was 0.3%, 2.5%, 9.6% and 25% in patients from 0-1, 2-3, 4-5, and ≥6 points respectively (Table 6).

Using a cutpoint of 4 points, 78% and 83% of patients were correctly classified for CTLS and LTLS, respectively (sensitivity, 89% and 71%, respectively).

Discussion and conclusions

This study shows that TLS is frequently observed in AML patients during induction therapy. Nevertheless, only one third of patients who met LTLS criteria developed CTLS, that is the form of TLS in which was observed a higher induction mortality. In spite of the current preventive and therapeutic measures the observed TLS-related mortality was 2%. Introduction of prophylactic rasburicase will probably reduce the incidence and severity of CTLS during cytolytic therapy. However, its use may be cost effective in patients at high risk of developing CTLS.

We found that increased pretreatment LDH, uric acid, WBC, and creatinine levels were related to a higher incidence of CTLS. Using these parameters, we constructed a predictive model in which patients are divided in four CTLS-risk groups according to their individual calculated score at diagnosis: (1 Low risk: 0-1 points, (2 Standard risk: 2-3 points, (3 High risk: 4-5 points, and (4 Very high risk: ≥6 points.

High and very high CTLS-risk patients are obvious candidates for prophylactic rasburicase. In this subgroup of patients, use of prophylactic rasburicase may be cost-effective, since they only represent a quarter

of AML population. In addition, following this risk adapted strategy 89% of patients that developed CTLS should have received prophylactic rasburicase.

Low and standard CTLS-risk patients can be treated with oral allopurinol, but those with standard risk must be monitored by frequent biochemistry tests searching for TLS development.

In conclusion, we have developed a predictive model using a scoring system to identify patients according to the risk of CTLS. This model should be useful to design risk-adapted prophylaxis for TLS. However, this model needs to be validated on external prospective or retrospective observations.

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