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Identification of children with acute lymphoblastic leukemia at low risk for tumor lysis syndrome

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Abstract

Background and Objective: Tumor lysis syndrome (TLS) could occur before, during or after the initiation of chemotherapy in patients with cancers especially those with hematologic malignancies. This study was designed to determine the prevalence and predictors of TLS in children with Acute Lymphoblastic Lymphoma (ALL) and to develop a sensitive prediction rule to identify patients at low risk of TLS.

Methods: In this cross-sectional study 160 children diagnosed by ALL in Ali-Asghar Children Hospital, Tehran (1996-2010) were recruited. TLS was defined as having two or more of the certain criteria. Predictors of TLS were determined using univariate and multiple logistic regression analyses.

Results: TLS was diagnosed in 41 cases (25.6%). The most common laboratory abnormality was hypocalcaemia (30%) in these patients. The results of univariate analysis showed that splenomegaly (OR, 2.38; p=0.005), mediastinal mass (OR, 4.45; p=0.003), T-cell phenotype (OR, 4.66; p=0.001), central nervous system involvement (OR, 10.93; p=0.001), lactate dehydrogenase ≥2000 U/L (OR, 3.88; p=0.003), and white blood count (WBC) ≥20×109/L (OR, 4.18; p<0.001) were predictors of TLS in these cases. Multiple regression analysis of variables that were available at presentation identified CNS and renal involvement, mediastinal mass, and initial WBC ≥ 20 × 109/L as independent predictors of TLS. When all 4 of those predictors were absent at presentation (n= 83 patients), the negative predictive value of developing TLS was 92.22%, with a sensitivity of 82.93%.

Conclusions: It could be suggested to evaluate the risk of TLS in all patients with hematologic malignancies before starting chemotherapy. Finding a model of independent factors to define a group of ALL children at low risk of TLS could be used to prevent the monitoring and high cost prophylactic treatment modalities.

Keywords: Tumor lysis syndrome (TLS), Acute Lymphoblastic Lymphoma (ALL), Hypocalcemia

Introduction

There has been recognized a risk of developing Tumor lysis syndrome (TLS) after or before the initiation of conventional therapies such as chemotherapy, radiotherapy or immunotherapy in patients with acute lymphoblastic leukemia (ALL) and Burkitt lymphoma; or it could be started spontaneously (1-6). This life threatening syndrome is characterized by hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia which are the result of massive necrosis or apoptosis of large proliferating tumors, cell lysis and the metabolism of excessive nucleic acids. TLS occurs in 5-20% of cancer patients, but prophylactic approaches should be applied to prevent serious complications (1-5, 7, 8).

On the other hand, clinical TLS is defined by the presence of the above laboratory abnormalities and one or more clinical complications such as: renal insufficiency, cardiac arrhythmias/sudden death, and seizure (2, 9).

High tumor growth rate, as seen in Burkitt's lymphoma, lymphoblastic lymphoma, B-cell acute lymphoblastic leukemia (B-ALL), and T-cell ALL with hyperleukocytosis and/or extensive extramedullary disease predispose the patient to developing TLS.

Tumors with high sensitivity to chemotherapy and large tumor burden could be important factors of TLS progression in patients with solid tumor (2, 10).

Those with elevated serum level of lactate dehydrogenase (LDH) and decreased urinary flow rate are at a higher risk of TLS. Older patients with impaired renal function may predispose to clinically significant TLS. There has been reported no preference regards to the sex or race (2).

Several studies have been designed to determine high risk patients for TLS but identifying low risk group is also important regards to the expensive and unavailable treatments.

The aim of this study was describing the risk factors and predictors of TLS in pediatrics with ALL and approaching a sensitive model to identify those in lower risk.

Methods

In this cross-sectional study 160 children diagnosed by Acute Lymphoblastic Lymphoma (ALL) in Ali-Asghar Children Hospital, Tehran (1996-2010) were recruited. Those with incomplete data, treated in other centers at the first steps, not treated by the primary treatment of ALL, those who were transferred to the other centers at the certain duration (admission time up to the 7th day of treatment), ALL classified as L3 in French-American-British (FAB) classification (Burkitt Leukemia) were excluded from the study.

TLS was defined as having two or more of the following criteria (10):

- Hyperurecemia (Uric acid > 8 mg/dL)
- Hyperkalemia (Potassium > 5.5mEq/L)
- Hyperphosphatemia (Phosphorous > 7 mg/dL)
- Hypocalcemia (Calcium< 8mg/dL)
- Renal Failure (Serum creatinin > 1.5 of normal limits for the age)

Potential Predictors Evaluated

Laboratory data such as WBC and LDH were collected at admission time. Clinical markers of bulk disease were reviewed by physical examination at the same time as followings: mediastinal mass on chest X-rays, hepatomegaly (palpable liver ≥ 3 cm below the right costal margin), and splenomegaly (palpable spleen ≥ 2 cm below the left costal margin). Central nervous system (CNS) status and renal involvement by leukemia (diagnosed by renal enlargement on abdominal imaging studies) were other predictors which were evaluated. Regards to the previous publications, a cutoff value of 2000 U/L was chosen for LDH. The initial serum level of potassium, phosphate, creatinine, uric acid, and calcium were not assumed as potential predictors, regards to the incorrect methodology, in that those values would contribute toward the definition of the outcome (development of TLS).

All enrolled patients with precursor B-cell ALL received the BFM protocol (conventional/IC BFM 2002). They received oral prednisolone 30 mg/m^2/day for the 7th days of starting chemotherapy plus IT MTX on the first day. All enrolled patients with T-cell ALL were treated by LSA2L2/NY-1 protocol. They received Cyclophosphamide 400 mg/m^2/d for the first 3 days plus IT ARAC following with oral prednisolone 30 mg/m^2/day divided into 3 doses or dexamethasone 6 mg/m^2/d divided to 2 or 3 dose until 7th days of starting chemotherapy.

Univariate analysis and Chi-square were used to evaluate the relationship between variables and the risk of TLS. Those with a p-value<0.05 was considered as the predictors of TLS. Those predictors of low risk for TLS with a P-value < 0.1 were entered into the multiple logistic regression analysis by forward-LR method.

Study protocol was approved by the local ethical committee and informed consent was taken from the parents. All entered patients in this study had to meet the approved protocol and consent requirement based on the full understanding of the study design.

Results

One hundred and sixty children were included in this study with a mean (±SD) age of 5.38 (± 3.55) years (max=14 years and min=7 months). Demographic characteristics, clinical and laboratory data of the studied population are shown in Table 1.

Among them TLS was presented in 41 (25.6%). The most common laboratory abnormality in all patients was hypocalcaemia (48 cases=30%). The least frequent laboratory abnormality was hyperphosphatemia (16 cases=10%). The most common laboratory abnormality pair for TLS was hypocalcemia and hyperphosphatemia (10 of 160 patients; 6.25%), followed by concurrent abnormalities of calcium and uric acid (5.6%). The peak laboratory values of potassium, phosphate, uric acid, and creatinine as well as the calcium were 8.7 meq/l, 11.1 mg/dl, 35.7 mg/dl, 6.6 mg/dl and 4.3 meq/l, respectively.

The results of univariate analysis which are shown in table 2 showed that CNS and renal involvement and T-cell immunophenotype are among the strongest predictors of TLS in these cases. The initial LDH value was a strong predictor of TLS;

Table 1. Demographic background, clinical and laboratory distribution

Variables		Numbers (%) N= 160
Gender	Male	91 (56.9)
	Female	69 (43.1)
Age (≥10 years)		28 (17.5)
Primary WBC ≥20.000/µL		54 (33.75)
Significant splenomegaly		67 (41.87)
Significant hepatomegaly		46 (28.75)
Mediastinal mass		17 (10.62)
CNS involvement		8 (5.0)
Renal involvement		15 (9.37)
Baseline LDH ≥2000 U/L		27 out of 108 (25)
ALL	T-cell	22 (13.8)
immunophenotype	Precursor B-cell	138 (86.2)

Table 2. The predictors of TLS in pediatrics with ALL in Univariate analysis

Variables	TLS + (n=41)	TLS – (n=191)	p	95% CI	OR
Baseline WBC≥20000/µL	24 (58.5%)	30 (25.2%)	< 0.001	1.98-8.83	4.18
Splenomegaly	25 (61%)	42 (35.6%)	0.005	1.36-5.87	2.38
Hepatomegaly	18 (43.9%)	28 (23.5%)	0.013	1.2-5.37	2.54
Mediastinal mass	9 (25.7%)	8 (7.2%)	0.003	1.56-12.67	4.45
Renal involvement	10 (25%)	5 (4.2%)	< 0.001	2.41-23.91	7.6
CNS involvement	6 (16.25)	2 (1.7%)	0.001	2.10-56.87	10.93
T-cell immunophenotype	11 (28.9%)	9 (8%)	0.001	1.75-12.39	4.66
Baseline LDH ≥2000 U/L	16 (19.8%)	11 (4.7%)	0.003	1.52-9.89	3.88
Age ≥ 10 yr	10 (24.4%)	18 (15.1%)	0.18	075-4.32	1.81
Male sex	20 (48.8%)	71 (59.7%)	0.23	0.76-3.17	1.55

however, because only 108 LDH samples were determined on the day of presentation to hospital, this variable could not be included in the multiple regression analysis.

Age at diagnosis and sex were not statistically significant predictor of TLS in this study. Of the remaining 5 variables (WBC, mediastinal mass, hepatomegaly, splenomegaly, and T-cell immunophenotype), 4 variables were identified in multiple regression as independent predictors of TLS: mediastinal mass, initial WBC $\geq 20x10^9$/L, CNS and renal involvement at diagnosis (Table 3).

The absence of all 4 predictors of TLS was used to define a group at low risk of developing TLS (the low-risk TLS group). Of those who fulfilled low-risk TLS criteria, 83 of 90 patients did not develop TLS, resulting in a negative predictive value of 92.22% (95% CI, 84.81–96.18%) and a sensitivity of 82.93% (95% CI, 68.74–91.47%).

Table 3. The independent predictors of TLS in multivariate logistic regression analysis

Variables	95% CI	OR	p
CNS involvement	1.88-71.80	11.61	0.008
Renal involvement	2.30-28.33	8.07	0.001
Mediastinal mass	1.34-14.02	4.34	0.014
WBC≥ 20,000/µL	1.33-7.28	3.11	0.009

Discussion

Tumor Lysis Syndrome (TLS) is a critical consequence of cancer therapy and delayed diagnosis could result in life threatening conditions and even patient death. So earlier recognition and appropriate treatment is crucial (5, 11).

There had been considered some modifiable risk factors for TLS which could be prevented such as: dehydration of cancer patients especially before the chemotherapy and the concomitant treatment of nephrotoxic medications and other ones (4, 11). Elevated serum level of uric acid before the treatment, prior renal insufficiency, tumor infiltration in the kidney or obstructive uropathy, and advanced age are known comorbidities predisposing patients to higher risk of developing TLS (4, 12). It has been recommended to apply prophylactic approaches in all pediatrics or adults suffered from hematologic malignancies undergoing chemotherapy (4, 11, 13).

In the present study about 25% of ALL patients met TLS criteria and in univariate regression model, CNS and renal involvement, T-cell immunophenotype and initial WBC≥ 20000/µl were among the strongest predictors of TLS in these cases. Although the initial LDH value was a strong predictor of TLS but it was not available in all cases and did not entered into the predictive model. There was no sex or age preference. Then only potential predictors

available at the admission time were entered into multivariate logistic regression analysis consisted of mediastinal mass, initial WBC ≥20x10^9/L, CNS and renal involvement. In the latter model negative predictive value (NPV) was 92.22% (95% CI, 84.81–96.18%) and a sensitivity of 82.93% (95% CI, 68.74–91.47%).

Truong et al in a study in Canada (2007) recruited 328 children aged ≤ 18 years who were diagnosed with ALL. Results showed that among these pediatric patients 23% met criteria for TLS. Factors predictive of TLS were male sex (odds ratio [OR], 1.8; P=5.041), age≥ 10 years (OR, 4.5; P <0.0001), splenomegaly (OR, 3.3; P < .0001), mediastinal mass (OR, 12.2; P <0 .0001), T-cell phenotype (OR, 8.2; P< 0.0001), CNS involvement (OR, 2.8; P=5.026), lactate dehydrogenase ≥2000 U/L (OR, 7.6; P< 0.0001), and white blood count (WBC) ≥20 × 10^9/L (OR, 4.7; P< 0.0001). Among available independent variables at presentation, age ≥10 years, splenomegaly, mediastinal mass, and initial WBC ≥20 × 10^9/L were recognized as predictors of TLS in multivariable analysis. The negative predictive value of developing TLS in this model was 97%, with a sensitivity of 95% (1). The initial LDH value was a strong predictor of TLS, because only 33 LDH samples were determined on the day of presentation to hospital, this variable could not be included in the multiple regression analysis. In our study, children older than 10 years consisted a low fraction of the studied group and male to female ratio was almost equal so these two factors were not significant in predicting the risk of TLS and the NPV and sensitivity of our study model was slightly lower than this.

Beyene et al in a study to determine the validity of predicting models concluded that age is the most important predictor of TLS and the second most important variable is WBC. They reported that a group at low risk of TLS consists of children younger than 10 years of age, without T-cell immunophenotype, whose baseline WBC is < 20 × 10^9/L and palpable spleen is < 2 cm (14). As mentioned before in the present study age was not a significant predictor in TLS.

Wössmann et al in a study on 1791 children with B type ALL or stage III/IV Burkitt's lymphoma and LDH level ≥ 500 U/L analyzed the prevalence and complications of TLS during the first two weeks of admission. During the time of study, the prophylactic treatment of TLA with urate oxidase was performed in some of them but the initial chemotherapy was identical. TLS was reported in 78 children (4.4%). Patients with B-ALL had the highest risk to develop a TLS (26.4%) followed by B-ALL/Burkitt's lymphoma and a LDH > or =500 U/l (14.9%). They suggested that patients with the highest risk of developing TLS could benefit from the prophylactic use of urate oxidase. They considered a lower range of LDH as the threshold to be risky for TLS (500 versus 2000 in our study) and there was a limitation studying those with B-type ALL and no case of T-type (15). In the present study, LDH was diagnosed as a strong predictor of TLS but it was not entered into the prediction model because it was not available at presentation in all cases.

Hesham et al studied 60 ALL children and adolescents younger than 18-years and concluded that the strongest predictors of TLS are as followings: high intial WBC ≥ 20 x10/L, followed by T-cell immunophenotyping and then intia LDH ≥ 1000 IU/L, and splenomegaly. In their findings 6 cases (10%) were at the low risk group and had no TLS and they mentioned that if a patient has no factors of the above ones he/she would not progress TLS (16).

Our study is important from several points of view. First of all it is among the very first studies done for early identification of ALL in pediatrics with low risk of TLS. Second, this could decrease the cost to benefit ratio to monitor and treat prophylactically in this group and is a crucial step in under developing countries with lower socio-economic status. On the other hand, it could result in decreasing monitoring, blood sampling and damaging peripheral vessels in children and preventing the imposed cost of expensive drugs like Rasburicase. It maybe question some prophylactic approaches like alkalinizing the urine.

Although it seems that approaching a comprehensive, perfect, high sensitivity and high negative predictive value (NPV) predictive model needs a prospective large study with acceptable sample size considering the initial LDH besides all other factors.

Conclusions

The risk of TLS could be evaluated in all patients with hematologic malignancies before starting chemotherapy. Finding a model of independent factors to define a group of ALL children at low risk of TLS could be used to prevent the monitoring and high cost prophylactic treatment modalities.

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