

Tumour Lysis Syndrome in children with haematological cancers: Experience at a tertiary care hospital in Karachi

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Abstract

Objective: To determine the incidence of tumour lysis syndrome and to identify associated factors and mortality rate in paediatric haematological patients.

Methods: The prospective study was conducted from April to September 2016 at Indus Children Cancer Hospital, Karachi, and collected data for all new paediatric oncology patients registered with diagnosis of haematological malignancies. Each patient was monitored for a period of three days before and seven days after the start of the treatment. SPSS 21 was used for data analysis.

Results: of the 232 patients, 86(37.1%) developed laboratory tumour lysis syndrome and 35(40.7%) of these patients developed the spontaneous variety. Overall, 24 (10.3%) patients progressed to clinical syndrome with 12(50%) of them developing spontaneous clinical syndrome. Mortality occurred in 17 (7.3%) patients.

Conclusion: Despite preventive measures, tumour lysis syndrome remains an oncological emergency in children with haematological malignancies.

Keywords: Haematological malignancies, Tumour lysis syndrome, TLS, Spontaneous tumour lysis syndrome, Laboratory tumour lysis syndrome, LTLS, Clinical tumour lysis syndrome, CTLS. (JPMA 68: 1625; 2018)

Introduction

Cancer is one of the leading causes of mortality worldwide.¹ Globally, in children less than 15 years of age, around 160,000 new cancer cases and 90,000 cancer deaths are estimated to occur each year.² Children constitute over one-third of the total population in developing countries and childhood cancers represent 3-10% of the total compared to nearly 1% in the developed regions.² Incidence of childhood cancer in Pakistan has been reported as 100 per million population. Among them, the incidence of leukaemia and non-leukaemia cancers are 40.5 per million and 59.5 per million respectively.³ Treatment of cancer includes multimodality regimen, and chemotherapy is the widely used treatment option. Exposure to chemotherapy, besides killing the tumour cells, also causes a metabolic disorder named tumour lysis syndrome (TLS).⁴ TLS is the most common cancer-related emergency

encountered in children and adults of all ages.⁵ It is characterised by hyperphosphataemia, hypocalcaemia, hyperkalaemia, hyperuricaemia, and often acute renal failure (ARF) requiring immediate treatment and supportive care to decrease the risk of associated morbidity and mortality.⁶

TLS can occur in solid organs' cancers but is most commonly observed with haematological cancers such as acute lymphoblastic leukaemia (ALL) and high-grade non-Hodgkin lymphoma (NHL), in particular Burkitt's lymphoma.⁷ In patients with acute leukaemia, TLS can be a life-threatening complication during the induction phase of rigorous chemotherapy with deranged values of uric acid, potassium, phosphate and calcium levels in blood, leading to nephropathy.⁸⁻¹⁰ The clinically significant disturbance in metabolic function associated with TLS can be observed within 48-72 hour of induction chemotherapy.¹¹⁻¹⁴

A study divided TLS into Laboratory TLS (LTLS) and Clinical TLS (CTLS) in order to distinguish between patients who do not require rigorous therapeutic management versus

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those who experience life-threatening situation and require immediate treatment.¹⁵ The Cairo and Bishop model, which is the most commonly used criteria for the diagnosis of TLS,⁷ defines LTLS as the presence of at least two serum metabolic derangements in serum uric acid, potassium, phosphorus or calcium whereas CTLS is an extension of LTLS in which there is an addition of at least one clinical manifestation such as seizures, arrhythmias, increase in serum creatinine or sudden death. These events must occur either three days before or seven days after the initiation of chemotherapy.^{13,16} Furthermore, the occurrence of TLS can be spontaneous or after initiation of treatment.¹⁵ Spontaneous TLS (STLS) refers to the manifestation of TLS in patients who have not undergone the cytotoxic therapy.¹⁷

The incidence of TLS reported by a study conducted among patients with high-grade non-Hodgkin lymphoma was 42%, of which CTLS was observed in 6% of the sample.⁷ The study only included patients with TLS post-chemotherapy, not taking into account those with STLS. Another study conducted in Pakistan among adult patients of haematological malignancies found TLS in 20% patients. Of these, 60% developed LTLS while 40% developed CTLS.¹⁸ Similarly, a study of 1971 children with advance stage Burkitt's lymphoma and leukaemia found TLS in 4.4% of the sample where patients diagnosed with B-cell acute lymphoblastic leukaemia (B-ALL) had the highest risk of TLS (26.4%).¹⁰

Risk factors for TLS include high tumour cell proliferation rate, large tumour burden, sensitivity of tumour to chemotherapy and increased lactate dehydrogenase (LDH) levels. Other factors include hypotension, dehydration, acidic urine, oliguria, pre-cancer nephropathy and previous experience with nephrotoxic agents along with those medications and compounds that are likely to increase the uric acid levels.¹⁷

The management of TLS includes early identification of at-risk patients as most of the complications can be readily managed if identified early.¹³

Literature suggests that serum creatinine, blood urea nitrogen, sodium, potassium, calcium, phosphorous, LDH and uric acid levels should be determined before therapy and every 4-6 hours for the first 48-72 hours post-initiation of therapy.¹³ Patients should also have a baseline electrocardiography (ECG) and continuous cardiac monitoring until the completion of treatment. All patients

should receive intravenous (IV) hydration for 24 to 48 hours.¹³

Literature on TLS incidence is scarce and has mainly focussed on few proliferative cancers or the adult population. In Pakistan, there is limited published literature on the incidence of TLS in all haematological malignancies in paediatric patients. Haematological malignancies account for almost 50% of the cases seen at paediatric oncology department of the Indus Hospital in Karachi. Approximately 500 paediatric cancer patients are treated annually with approximately 60 admissions per month.

The current study was planned to determine the incidence of TLS along with identifying the associated factors and mortality rate among paediatric haematological cancer patients.

Patients and Methods

The prospective study was conducted from April to September 2016 at Indus Children Cancer Hospital, Karachi, and collected data for all new paediatric oncology patients registered with diagnosis of haematological malignancies receiving prophylaxis treatment of allopurinol and hydration. The sample size was calculated using Openepi software with assumed prevalence of TLS being 11.6%, and confidence limits being 4%.¹⁹ The required sample size was 247.

After approval was obtained from the institutional review board, patients were included in the study if they were up to 16 years of age, newly diagnosed with leukaemia including ALL, acute myelogenous leukaemia (AML), chronic lymphocytic leukaemia (CLL), chronic myelogenous leukemia (CML) as well as other leukaemia, or lymphoma including Hodgkin lymphomas (HL) or Non-Hodgkin lymphomas (NHL). Patients were excluded if they were previously diagnosed with haematological cancer, were already on treatment, or were treated before. Also excluded were those diagnosed with solid tumours, including carcinomas and sarcomas.

Patient-related information was collected by the duty bed doctors who were trained on filling the pre-designed forms which included registration, eligibility and clinical assessments. The registration form recorded demographic characteristics such as age, gender, height, weight and diagnostic information. The hospital's electronic health management information system (HMIS) was used to extract clinical parameters starting from three days before

the treatment initiation and for seven days post-treatment. These clinical parameters included serum calcium, phosphorus, uric acid, creatinine and potassium levels. Clinical information was also documented for complications such as seizures, cardiac arrhythmias or sudden death.

All the patients were monitored for LTLS and CTLS as per the Cairo-Bishop definition.⁷ LTLS was considered positive if the presence of two or more of the laboratory changes were observed 3 days before or 7 days after initiation of chemotherapy. The precautions used pre-emptively were close monitoring in intensive care unit (ICU) and high dependency unit (HDU), IV fluid hydration (3000ml/m²/24hours), prophylactic allopurinol in a dose of 300mg/m²/day in three divided doses, restricted intake and output monitoring, preventing hyperkalaemia and hyperphosphataemia. Urinary alkalinisation was avoided. Lab changes included uric acid $\geq 476 \mu\text{mol/L}$ (8 mg/dL) or 25% increase from baseline, potassium $\geq 6.0 \text{ mmol/L}$ (6mEq/L) or 25% increase from baseline, phosphorous $\geq 2.1 \text{ mmol/L}$ or 25% increase from baseline and calcium $\leq 1.75 \text{ mmol/L}$ or 25% decrease from baseline. Patients developing LTLS who also displayed elevated serum creatinine that is > 1.5 times the institutional upper limit of normal (ULN), or the presence of cardiac arrhythmia, seizures or sudden death were diagnosed with CTLS.

The data was entered and analyzed using SPSS 21. Distribution of the variables was assessed using the rule of thumb where if the skewness statistics lay between -2 to +2, the distribution was considered reasonably normal. Continuous variables such as age, height and weight were reported as mean $\pm$ standard deviation (SD) while the categorical variables, such as types of malignancies, presence of deranged biochemical parameters, LTLS and CTLS, were reported as frequencies along with percentages. Various variables such as serum uric acid, potassium, phosphorus, calcium and creatinine levels were used to calculate the TLS considering the cut-offs and standard definition by Cairo and Bishop.⁷ Independent sample t-test was used to assess significant difference in age, height and weight between TLS and non-TLS patients. Chi-square / Fisher-Exact / Likelihood-ratio and chi-square test were used as appropriate to assess significant association between different predictors such as gender, status of survival and haematological malignancies with CTLS and non-CTLS patients. $P < 0.05$ was considered significant.

Results

Of the 232 patients, 156 (67.2%) were boys. The overall mean age was 7.8 ± 4.1 years (range: 0.8-16 years). The mean height and weight of the patients were $119 \pm 24.9 \text{ cm}$ and $21.9 \pm 11.1 \text{ kg}$ respectively. Overall, 86(37.1%) children developed TLS. LTLS was evident in 35 (40.7%) patients. A total of 24 (10.3%) patients progressed to CTLS with half of them developing SCTLS. Mortality occurred in 17(7.3%) patients (Table-1). None of the patients required dialysis because of early identification and prompt management of biochemical abnormalities with increased hydration and allopurinol. No side effects, like rash, neuritis, hepatotoxicity, gastrointestinal disturbances, bone marrow suppression and drowsiness were observed.

Among different types of haematological cancers, 129(55.6%) were ALL, followed by 45(19.4%), AML, 30 (12.9%) HL and 24(10.3%) (NHL). There were 105(81.4%) B-ALL patients. Among the NHL category, 16(66.7%) patients had B-NHL. The least observed cancer was chronic leukaemia with only 4(1.7%) patients (Table-2).

Table-1: Demographic characteristics of the Paediatrics patients with Haematologic cancers.

Characteristics	
Age (Years): mean $\pm$ SD	7.8 $\pm$ 4.1
Height (cms): mean $\pm$ SD	119 $\pm$ 24.9
Weight (Kg): mean $\pm$ SD	21.9 $\pm$ 11.1
Gender	n (%)
Male	156 (67.2)
Female	76 (32.8)
TLS Incidence	n (%)
Laboratory TLS (LTLS)	86 (37.1)
Spontaneous LTLS	35 (40.7)
Clinical TLS (CTLS)	24 (10.3)
Spontaneous CTLS	12 (50.0)
Mortality	17 (7.3)

TLS: Tumour lysis syndrome. SD: Standard deviation.

Table-2: Cancer Related Characteristics of the Pediatric patients.

Tumors	n (%)
Acute Lymphoblastic Leukemia (ALL)	129 (55.6)
B Cell-ALL	105 (81.4)
T Cell-ALL	24 (18.6)
Acute Myeloblastic Leukaemia	45 (19.4)
Acute Myeloid Leukaemia (AML)	40 (88.8)
Acute Promyelocytic Leukaemia (APML)	5 (11.1)
Chronic Leukemia	4 (1.7)
Chronic Lymphocytic Leukaemia (CLL)	1 (25)
Chronic Myeloid Leukaemia (CML)	3 (75)
Hodgkin Lymphoma	30 (12.9)
Non- Hodgkin Lymphoma (NHL)	24 (10.3)
B Cell-NHL	16 (66.7)
T Cell-NHL	8 (33.3)

Table-3: Biochemical Parameters among Paediatric Patients with Haematological Cancers.

Biochemical Parameters (n=232)	n (%)
Calcium (≤ 7 mg/dl) or (25% $\downarrow$ from baseline)	33 (14.2)
Phosphorus (≥ 6.5 mg/dl)	114 (49.1)
Potassium (≥ 6 mEq/L) or (25% $\uparrow$ from baseline)	61 (26.3)
Uric Acid (≥ 8 mg/dl) or (25% $\uparrow$ from baseline)	74 (31.9)
Creatinine (> 1.5 times upper limit of age adjusted reference range)	18 (7.8)

Table-4: Factors Associated with Clinical Tumour Lysis Syndrome.

Variables	CTLS (n=24) n (%)	Non-CTLS (n=208) n (%)	p-value
Gender			0.69†
Male	17 (70.8)	139 (66.8)	
Female	7 (29.2)	69 (33.2)	
Haematological Malignancies	14 (58.3)	115 (55.3)	
Acute Lymphoblastic Leukaemia	3 (12.5)	42 (20.2)	0.016*‡
Acute Myeloblastic Leukaemia	1 (4.2)	3 (1.4)	
Chronic Leukaemia	0 (0)	30 (14.4)	
Hodgkin Lymphoma	6 (25)	18 (8.6)	
Status of Survival			
Deceased	11 (45.8)	6 (2.9)	<0.0001**†
Alive	13 (54.2)	202 (97.1)	
Age (mean $\pm$ SD)	8.6 $\pm$ 4.9	7.7 $\pm$ 4.0	0.27‡
Height (mean $\pm$ SD)	123.5 $\pm$ 29.2	118.5 $\pm$ 24.24	0.351‡
Weight (mean $\pm$ SD)	25.0 $\pm$ 14.9	21.6 $\pm$ 10.6	0.168‡

p-value <0.05, *P-Value <0.0001, †Chi-square test, ‡Likelihood ratio chi-square test, ^ fisher exact test, §independent t-test.

CTLS: Clinical tumour lysis syndrome.

SD: Standard deviation.

An increase in serum uric acid concentration was observed in 74 (31.9%) patients. The levels of serum phosphate were found to be equal to or more than 6.5mg/dL in 114 (49%) patients. A 25% decrease in serum calcium level from baseline or serum calcium level of ≤ 7 mg/dL was observed in 33 (14.2%) patients. Furthermore, the serum potassium level of ≥ 6 mEq/L or a 25% increase from baseline was observed in 61 (26%) patients. Creatinine, an important indicator for the CTLS was raised in 7.8% patients (Table 3).

When factors were analysed for their association with CTLS, different types of haematological malignancies and statuses of survival were found statistically significant ($p < 0.05$). There was no association between gender, age, height, and weight and TLS (Table-4).

Discussion

TLS has been reported in high-grade and aggressive cancers such as acute leukaemia and NHL.²⁰ Majority of the studies report that TLS involves patients with haematological

cancers and that paediatric population is at considerable risk of developing TLS during the course of treatment.¹⁶

In our study, the overall incidence of TLS found in haematological cancers was 37%, of which 10.3% progressed to CTLS. In comparison, a retrospective study on paediatric patients with haematological malignancies, reported the TLS incidence of 11.4% with 8.5% of patients fulfilling the CTLS criteria.¹⁶ They found no case of TLS before the start of chemotherapy which is in contrast to our study where spontaneous LTLS was observed in 40% of the patients while 50% patients developed CTLS spontaneously. The rates shown by our study are comparatively higher.

Local studies evaluating incidence of TLS among all paediatric haematological malignancies are scarce. Mostly reported incidences are from the international paediatric or adult cancer samples or they are focussing on a single type of malignancy. A local study conducted in Karachi among adult patients with haematological malignancies found an overall TLS incidence of 20%. Almost 60% of this was LTLS while 40% was CTLS. Among them 20% developed STLS. Death due to TLS was observed in 6% of the sample.¹⁸ A study among children with acute leukaemia found an incidence of 19% with no deaths observed.²¹ Likewise, in a study among adult AML patients, TLS was observed in 17% of the sample and 5% developed CTLS. Also, 25% of the patients had STLS while 75% developed TLS during the course of chemotherapy.²² Also, a study in NHL patients found an incidence of 42%, and among them 6% advanced to CTLS.²⁰ The incidence of TLS reported in a study among AML and ALL patients found an incidence of 20.8%.²³ In our sample, we found deaths in 7% of the patients. Mortality rate of 46% was found among patients with CTLS compared to 2.9% among patients who did not develop CTLS. The mortality rate found by our study is quite high which proves that TLS is an oncological emergency which requires constant monitoring.

The occurrence of TLS differs by the type of malignancy. Incidence of CTLS is reported to be approximately 3-7% in acute leukaemia and 4-11% in lymphomas.¹⁵ In a study, the incidence of TLS was 12.8% in ALL patients and 33% in Burkitt lymphoma patients. NHL patients developed TLS.¹⁶ A pan-European retrospective chart review identified TLS in 3.4% and 5.2% patients with AML and ALL respectively with an overall mortality of 0.9% for all patients and 17.5% for patients who developed TLS.²⁴ In our study, the incidences of TLS found in patients with ALL and AML were 10.8% and 6.7% respectively and among NHL patients, it

was 33.3%. No patient with HL developed TLS which is consistent with literature.¹⁶ Another study reported the incidence of TLS in children with B-ALL to be 26.4%. Similarly, another study reported 11.85% TLS incidence in NHL patients.⁶ Although these figures are comparable to our results, other studies have reported a substantially higher incidence of TLS. For example, the incidence of TLS found among NHL patients was 42%²⁰ and another study reported an incidence of 70%.²⁵

TLS is the result of metabolic derangement in which various biochemical alterations act together to give rise to this emergency. One study found 13.9% patients with hypocalcaemia, 12.6% with hyperuricaemia, 14.2% with hyperphosphataemia and 1.3% with hyperkalaemia. As opposed to that, our study found substantially higher derangement in these metabolic markers where 14.2% patients had hypocalcaemia, 49% hyperphosphataemia, 26.3% hyperkalaemia and 32% patients developed hyperuricaemia.¹⁶ In our study 75% patients developed acute kidney injury (AKI) with creatinine >1.5 times the upper limit which is comparable to 75% patients developing AKI in the earlier study.

A number of factors influence the risk of TLS, including the type of malignancy, rate of associated cell turnover, sensitivity to chemotherapy and type and intensity of treatment. Some studies have shown that the risk of TLS among men is higher compared to female.^{21,23} Our study did not show any significant association with gender. Other physical characteristics such as age, weight and height, did not show any significant association with TLS either. A study also found similar results regarding TLS, gender and age. Pre-treatment white blood cells count with TLS were also evaluated, but showed no significant association.⁶

Successful management of TLS is highly dependent on the rapid identification of clinical and laboratory characteristics and clinical manifestations of patients at risk. Formation of vascular access and the initiation of prophylactic measures, particularly hydration and administration of allopurinol, are vital in the prevention and management of TLS.¹³ The early recognition and treatment of metabolic abnormalities usually prevents the severe and life-threatening complications associated with TLS in immune-compromised cancer patients.¹³

Despite the limited duration of patient enrollment for 6 months, the prospective nature of the current study allowed for continuous monitoring and progress of paediatric TLS

patients for a period of 10 days. There is scarce data in Pakistan regarding paediatric TLS patients, and thus the study provides valuable information about TLS in a wide range of paediatric haematological malignancies. The incidence of TLS reported by the current study was considerably higher compared to other international researches. Due to the limited time duration, patient's from certain cancer categories were not equally represented. Therefore, a prospective study with a larger sample size can be planned to better evaluate the radiological findings and laboratory outcomes for understanding the concept of TLS and explain our findings of a higher incidence.

In spite of all preventive measures tumour lysis syndrome is still being reported in children with haematological malignancies. Vigilant monitoring is required to prevent the initiation and progression of patients from LTLS to CTLS.⁶ In the presence of highly effective treatment for prevention and management of TLS, it is very important to focus on the risk assessment in cancer patients. Provision of effective prophylactic therapy with effective dosage can be the difference between successful and unsuccessful outcome in at-risk patients.¹⁷

On the basis of our findings and in line with literature,²⁶ we recommend that patients with any haematological malignancy who are going to receive chemotherapy should have a risk assessment for TLS. High-risk patients should be treated prophylactically with increased hydration along with rasburicase with the exception of patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency and hypersensitivity to rasburicase. Such patients should be treated with fluids, allopurinol and careful monitoring. The recommended dose of rasburicase for prophylaxis in high-risk children is a single dose of 0.2 mg/kg, in the absence of established CTLS or LTLS. This should be followed by close laboratory and clinical monitoring for evidence of progressive TLS. There are no established recommendations for urinary alkalinisation in prophylaxis of TLS.

Conclusions

Despite the use of preventive measures, TLS in our setting was reported frequently. Vigilant monitoring and possible changes to treatment protocol to reduce further morbidity and mortality are the key steps in the management of the condition.

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