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Research Article

Frequency of Tumor Lysis Syndrome in Acute Leukaemia Patients Undergoing Chemotherapy

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Abstract: ***Introduction:*** Tumor lysis syndrome (TLS) is defined as the release of intracellular components into the bloodstream as a result of widespread malignant cell lysis, which can occur spontaneously or during antineoplastic therapy. The most frequent disease-related emergency that individuals with acute leukemia experience is TLS. Leukemia has a global incidence of 10–18 cases per 100,000 people annually. The prevalence of acute leukemia in Bangladeshi people is 28.3%. This study aimed to determine the prevalence of TLS in patients with acute leukemia receiving chemotherapy. ***Methods:*** This was a retrospective observational study conducted in the Department of Hematology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh, from July 2012 to June 2013. In our study, we included 120 patients with acute leukemia who were enrolled in the inpatient department of Hematology. ***Result:*** The mean age of our study patients was 47.2 ± 13.9 years with a male (65%) predominance. Among the patients, tumor lysis in ALL was seen in 52 patients, of which 29 patients (55.77%) had LTLS & CTLS was seen in 23 patients (44.23%). Tumor lysis in AML was seen in 19 patients, of which 13 patients (68.42%) had LTLS & CTLS was seen in 6 patients (31.58%). ***Conclusion:*** In our study, we found that TLS is a rather common side effect that arises during induction therapy for patients with AML. Just one-third of patients who fulfilled the LTLS criteria went on to develop CTLS, the kind of TLS with a greater induction mortality risk.

Keywords: Tumor lysis syndrome, Acute myeloid leukemia, Acute Lymphoblastic Leukemia, Frequency.

INTRODUCTION

Tumor lysis syndrome (TLS) is defined as the release of intracellular components into the bloodstream as a result of widespread malignant cell lysis, which can occur spontaneously or during antineoplastic therapy [1, 3]. The most frequent disease-related emergency that individuals with acute leukemia experience is TLS [4-6]. It can be a potentially fatal side effect for patients with acute leukemia receiving induction chemotherapy. TLS occurs when tumor cells leak their contents into the bloodstream, resulting in electrolyte imbalances that can cause seizures, cardiac arrhythmias, renal insufficiency, and death from multiple organ failure. These imbalances include hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia [7, 8]. Although spontaneous TLS occurring before the commencement of chemotherapy has also been described, clinically relevant TLS usually arises during induction chemotherapy [9, 10]. The Cairo & Bishop classification method divides TLS into two categories: clinical tumor lysis (CTLS) and laboratory tumor lysis (LTLS) [11]. Within three days before or seven days following the start of chemotherapy, LTLS is deemed positive if any two or more of the specified serum biochemical indicators are positive. TLS has no preference for any particular age or sex, and its occurrence varies according to the type of cancer. The development is more likely to occur when certain intrinsic tumor-related characteristics, such as a substantial tumor burden with a high rate of proliferation, elevated LDH levels, and tumor chemosensitivity, are present. According to Montesinos *et al.*, the reported incidence of TLS in AML is 17% (12% LTLS & 5% CTLS), according to a thorough examination of the international literature [12]. According to Truong *et al.*, the incidence of tumor lysis in acute lymphoblastic leukemia (ALL) is 23% [13].

TLS is typically treated with substantial hyperhydration, urine alkalinization, and allopurinol to reduce uric acid. Despite these precautions, TLS-related morbidity and mortality still affect a significant proportion of patients with hematologic malignancies

[14-16]. However, few TLS research have focused on patients with acute myeloid leukemia (AML) [17,18]. With the introduction of new medications into clinical practice, such as recombinant urate oxidase [19], for the prevention or treatment of TLS, there has been a renewed interest in characterizing the TLS-prone population. Although TLS is assumed to be infrequent in AML, risk factors for TLS have been extrapolated to AML from studies performed in individuals with lymphoid malignancies [15, 20, 21].

Thus far, no research has been done in Bangladesh to determine the frequency of TLS in acute leukemia, even though it is one of the most frequent oncological emergencies. Leukemia has a global incidence of 10–18 cases per 100,000 people annually, with white people having the greatest incidence and American Indians and Alaskan natives having the lowest. The prevalence of acute leukemia in Bangladeshi people is 28.3%. The purpose of this study was to determine the prevalence of TLS in patients with acute leukemia receiving chemotherapy to detect this life-threatening complication.

METHODOLOGY & MATERIALS

This retrospective observational study was conducted in the Department of Hematology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh, from July 2012 to June 2013. In our study, we included 120 patients with acute leukemia enrolled in the inpatient department of Hematology.

These are the following criteria to be eligible for enrollment as our study participants: a) Patients aged more than 18 years; b) Patients with acute leukemia; c) Patients who had received at least one prior chemotherapy were included in the study and a) Patients with any history of acute illness (e.g., renal or pancreatic diseases, ischemic heart disease, asthma, COPD, etc.); c) Patients who were willing to participate were excluded from our study.

Data Collection: Complete history and examination were done. Investigations including WBC (White blood cell count), ALC (Absolute lymphocyte count), LDH (Lactate dehydrogenase), β2-microglobulin, albumin, potassium, creatinine & uric acid were done. All information was collected on pre-designed Performa.

Statistical Analysis: All data were recorded systematically in preformed data collection form. Quantitative data like age & duration of acute leukemia were expressed as mean and standard deviation. Qualitative data like gender, type of acute leukemia, chemotherapy, TLS, LTLS & CTLS were expressed as frequency distribution and percentage. Statistical analysis was performed by using SPSS 13 (Statistical Package for Social Sciences). The Ethical Review Committee of Bangabandhu Sheikh Mujib Medical University approved the study.

RESULTS

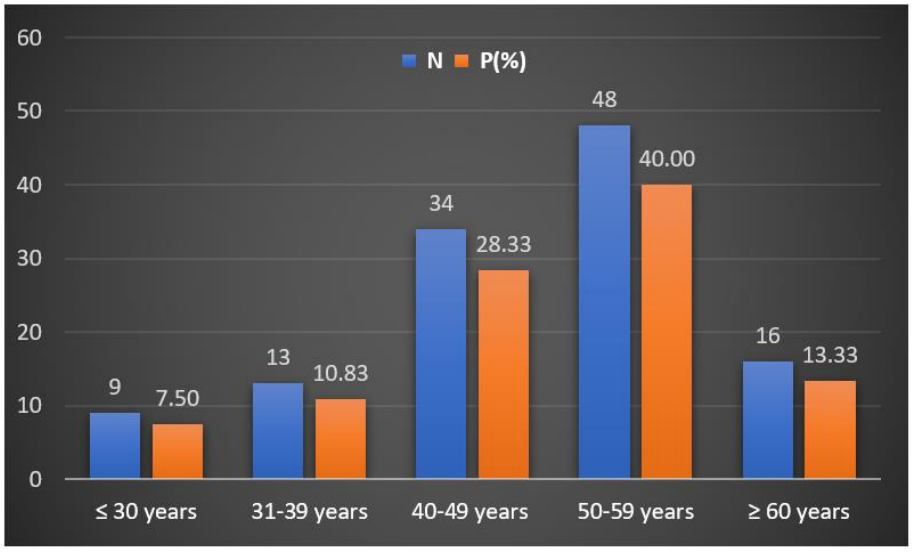

Figure 1: Age distribution of our study patients

Table 1 shows the majority (40%) of our patients were aged 50-59 years, followed by 28.33% of patients aged 40-49 years, 13.33% aged 31-39 years, 10.83% & 7.50% of patients aged ≥ 60 & ≤ 30 years respectively. The mean age was 47.2 ± 13.9 years.

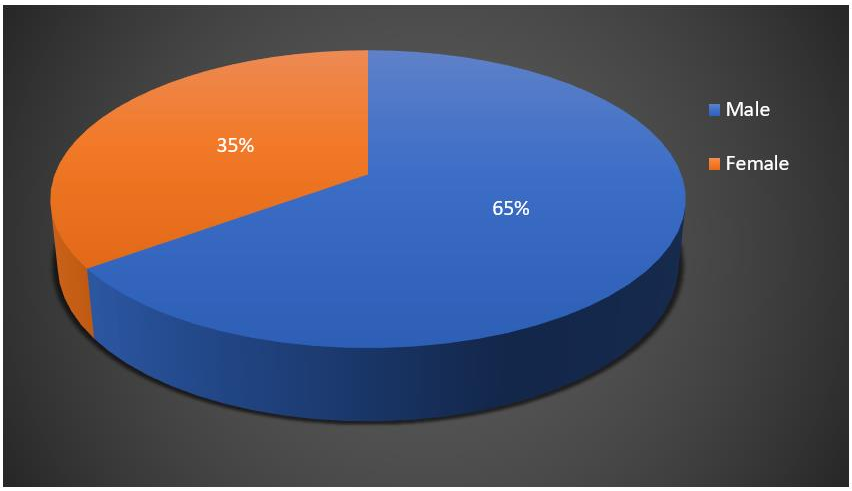

Figure 2: Gender distribution of our study patients

The pie chart shows the gender distribution among study patients. Among 120 patients, the majority (65%) of them were male and 35% were female. The male and female ratio was 1.86:1 in the study.

Table 1: Baseline characteristics of our study patients

Baseline	**N**	**P (%)**	**P-value**
Mean age (years)	47.2 ± 13.9		0.186
BMI (kg/m^2)	28.27±3.24		0.614
Types of acute leukemia			
Acute Lymphoblastic Leukemia (ALL)	72	60	
Acute Myeloid Leukemia (AML)	48	40	
Duration of acute leukemia (days)	6.17 ± 0.87		
Number of chemotherapies			
1	68	56.67	
>1	52	43.33	
WBC, × 10^9 /L Median (range)	24.1 (1.3-242.1)		<0.001
ALC, × 10^9 /L Median (range)	20.7 (0.7-239.3)		<0.001
Beta-2 Microglobulin, mg/L Median (range)	5.0 (0.8-15.4)		<0.001
LDH, U/L Median (range)	221 (103-504)		0.032
Albumin, mg/dL Median (range)	3.2 (2.0-4.6)		0.041
Potassium, mmol/L Median (range)	3.7 (2.4-4.8)		0.801
Creatinine, mg/dL Median (range)	1.05 (0.51-1.73)		0.614
Uric Acid, mg/dL Median (range)	5.2 (0.6-10.2)		0.720

BMI = body mass index, WBC: white blood cell count, ALC: absolute lymphocyte count, LDH: lactate dehydrogenase,

Table 1 shows the baseline characteristics of patients. The mean age was 47.2 ± 13.9 years, and the BMI averaged 28.27±3.24 kg/m² showed no significant difference (P=0.186, P=0.614, respectively). The majority 60% is Acute Lymphoblastic Leukemia (ALL) patients and 40% are Acute Myeloid Leukemia (AML). The duration of acute leukemia was 6.17 ± 0.87 days. A majority (56.67%) had undergone 1 chemotherapy, while 43.33% received more than 1. The WBC with a median range of 24.1 (1.3-242.1) (P<0.001) and ALC with a median range of 20.7 (0.7-239.3) (P<0.001). Beta-2 microglobulin with a median range of 5.0 (0.8-15.4) (P<0.001). LDH, U/L had a median of 221 (103-504) (P=0.032), and albumin had a median of 3.2 (2.0-4.6) (P=0.041). Potassium (P=0.801), creatinine (P=0.614), and uric acid (P=0.720) did not show significant differences.

Table 2: Frequency of tumor lysis syndrome (TLS) according to type of Leukemia (n = 120)

	Total	Tumor lysis syndrome (TLS)	Non- Tumor lysis syndrome
Acute Lymphoblastic Leukemia (ALL)	72 (60%)	52 (72.22%)	20 (27.78%)
Acute Myeloid Leukemia (AML)	48 (40%)	19 (39.58%)	29 (60.42%)
Total	120 (100%)	71 (59.17)	49(40.83%)

Table 2 shows that tumor lysis in ALL was seen in 52 patients (72.22%), and tumor lysis syndrome in AML was seen in 19 patients (39.58%). Non-tumor lysis syndrome was seen in 27.78% & 60.42% of patients in ALL & AML respectively.

Table 3: LTLS & CTLS according to type of Leukemia (n=71)

	LTLS		**CTLS**	
	N	**P (%)**	**N**	**P (%)**
ALL (n=52)	29	55.77	23	44.23
AML (n=19)	13	68.42	6	31.58
Total	42	59.15	29	40.85

ALL = Acute Lymphoblastic Leukemia, AML = Acute Myeloid Leukemia, LTLS = Laboratory Tumor Lysis Syndrome; CTLS = Clinical Tumor lysis Syndrome

Among all patients, tumor lysis in ALL was seen in 52 patients, of which 29 patients (55.77%) had LTLS & CTLS was seen in 23 patients (44.23%). Tumor lysis in AML was seen in 19 patients, of which 13 patients (68.42%) had LTLS & CTLS was seen in 6 patients (31.58%).

DISCUSSION

Our study showed that TLS is one of the common complications in patients diagnosed with acute leukemia especially observed during induction chemotherapy. We divided TLS into CTLS & LTLS and found that only one-third of our patients who met LTLS criteria developed CTLS, and the development of CTLS was associated with higher induction mortality.

There have been attempts to define and classify TLS consistently. Hande and Garrow divided TLS into LTLS and CTLS in 1993 [15]. However, these criteria did not cover patients who already had abnormal test findings. Cairo and Bishop extended the definition of LTLS to encompass changes in serum levels that are higher than normal, as well as changes that are more than 25% from baseline values, and that occur during the three days before and seven days after the start of chemotherapy to address this issue [22].

In our study, tumor lysis in ALL was seen in 52 patients (72.22%), and tumor lysis syndrome in AML was seen in 19 patients (39.58%). The incidence of CTLS in AML was 31.58%. Montesinos *et al.*, study found TLS in 130 patients (17%) of AML of whom 38 (5%) had CTLS and 92 (12%) had LTLS [23]. Patients with AML appear to have a lower incidence of CTLS than those with high-grade non-Hodgkin's lymphoma (NHL) or acute lymphoid leukemia (ALL), where the incidence varies between 11% and 25% [24-26].

The occurrence of LTLS in AML patients has not been thoroughly examined in several research. In 41 patients with hyper-leukocytic acute leukemia (WBC >100×10/L), Razis *et al.*, reported an incidence of LTLS of 57%, which was similar to the 59.15% observed in our investigation [27]. In a recently published series of 194 patients with AML or advanced myelodysplastic syndrome, [17] the incidence of LTLS was 10%. 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 [14,15].

Most previous AML research investigated TLS only after chemotherapy began, and none examined the incidence of spontaneous TLS. Likewise, in this study, 59.17% of the TLS cases (29 CTLS and 42 LTLS) occurred after chemotherapy. We discovered that the median day of onset of TLS was day +2 after the initiation of chemotherapy.

Furthermore, the development of CTLS was substantially related to a greater fatality rate after induction treatment, owing primarily to hemorrhage, TLS, or both. However, the establishment of isolated LTLS was not related to an increase in mortality during induction. The most prevalent laboratory findings of TLS in this investigation were elevated potassium and creatinine levels. This study found that high pretreatment LDH and creatinine levels are linked to an increased incidence of CTLS and LTLS in AML patients. This association between both parameters and the development of TLS has already been described in patients with AML. [28] We found a correlation between increased incidence of CTLS with raised pretreatment LDH, uric acid; WBC & creatinine levels and they were significant independent predictors of TLS which was also previously reported. [17,18] Remarkably, the independent risk factors for CTLS and LTLS were the same, but 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.

Therefore, early identification of risk patients with daily monitoring of serum biomarkers along with clinical signs and symptoms especially during the first 7 days of induction will be helpful in the early management of tumor lysis syndrome through prophylaxis treatment with allopurinol and rasbaricase [28,29].

Limitations of the study

Our study was a single-center study. We took a small sample size due to our short study period. After evaluating those patients, we did not follow up with them for the long term and did not know other possible interference that may happen in the long term with these patients.

CONCLUSION AND RECOMMENDATIONS

In our study, we found that TLS is a rather common side effect that arises during induction therapy for patients with AML. Just one-third of patients who fulfilled the LTLS criteria went on to develop CTLS, the kind of TLS with a greater induction mortality risk. Elevated pretreatment WBC counts, serum creatinine, uric acid, and LDH levels are the main indicators of CTLS and LTLS in AML patients. Our findings indicate that tumor lysis syndrome, one of the most frequent disease-related crises experienced by patients with acute leukemia, can be effectively treated with early identification of serum biomarkers and clinical manifestations.

So further study with a prospective and longitudinal study design including a larger sample size needs to be done to validate the findings of our study.

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Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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