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Incidence and Factors Predicting Laboratory Tumor Lysis Syndrome in Patients with Hematological Malignancies at Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia

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Abstract

Background

Tumor lysis syndrome is one of a catastrophic condition of multiple metabolic derangements that occur in bulk and rapidly dividing cancer. It is most commonly associated with hematological malignancies and results in significant mortality and morbidity. The aim of this study was to determine the incidence and factors predicting laboratory tumor lysis syndrome in patients with hematological malignancies.

Methods

A prospective cohort study was conducted on 49 patients diagnosed with hematological malignancies at Tikur Anbessa specialized hospital from September 2017 to April 2018. Data and blood sample were collected after getting written informed consent from the patients. Laboratory tumor lysis syndrome was assessed based on the Cairo and Bishop definition criteria using daily measured laboratory values of uric acid, potassium, phosphate and calcium. A regression analysis was used to assess the statistical association between incidence and factors predicting laboratory tumor lysis syndrome.

Results

The incidence of laboratory tumor lysis syndrome (LTLS) was 30.6% with 4.1% spontaneous and 26.5% new onset of LTLS. White blood cell count ≥ 25x109/L (AOR: 5.47, 95% CI: 1.11-26.96), lactate dehydrogenase level ≥2 times upper limit normal (AOR: 8.97, 95 % CI: 1.73-46.45) and age ≥ 60 years (AOR: 8.75, 95 % CI: 1.27-60.56) were independent factors predicting LTLS.

Conclusion

More than one-fourth of patients with hematological malignancies developed LTLS. Increased baseline white blood cell count, lactate dehydrogenase level and age were the main factors predicting LTLS.

Keywords: Tumor lysis syndrome; Hematological malignancy; Incidence; White blood cell count

Introduction

Tumor Lysis Syndrome (TLS) is one of a catastrophic condition of multiple metabolic derangements that occur in bulk and rapidly dividing cancer. It is characterized by metabolic derangements such as hyperkalemia, hyperphosphatemia, hyperuricemia and hypocalcemia (secondary to hyperphosphatemia). TLS usually develops from massive destruction of malignant cells after the initiation of cytotoxic therapies. Spontaneous TLS less commonly occurs in malignancies with a highly aggressive type of cell proliferation and rapid cellular turnover before treatment [1].

The massive cell destruction leads to a rapid release of intracellular components (potassium, phosphate and nucleic acids) to the extracellular environment. Nucleic acids are further metabolize to Uric Acid (UA). This exceeds the excretory capacities of the kidney and the biochemical changes can manifest clinically as renal, cardiac, and neural dysfunction. Hyperuricemia, the most common metabolic derangement which is caused by the release of tumor cell nucleic acids, can cause acute kidney injury (AKI) through the formation of crystals in renal tubules. Hyperkalemia can cause cardiac complications

that can lead to multiple organ failure and death. Hyperphosphatemia can lead to precipitation of calcium phosphate in the kidney which can cause obstructive nephropathy and AKI [2].

The various factors influencing the development of TLS includes type of malignancy, tumor burden (stage), Lactate Dehydrogenase (LDH) level, White Blood Cell counts (WBC), intensity of anticancer therapy, age, and the presence of preexisting conditions such as renal insufficiency, level of hydration, UA and creatinine level [3].

TLS is most commonly associated with Hematological Malignancies (HMs) such as Non-Hodgkin Lymphoma (NHL) and acute leukemia, particularly Burkitt's lymphoma/leukemia, Acute Lymphoblastic Leukemia (ALL), and Acute Myeloid Leukemia (AML). HMs particularly leukemia and lymphoma commonly proliferate and break down rapidly leading to a higher rate of TLS than other types of cancer. TLS incidence also varies widely in patients with HMs, depending on the type of malignancies, the variability of patient study duration, different diagnostic criteria, patient demographics and other characteristics [4].

TLS was first defined by Hande and Garrow and Cairo and Bishop modified this definition in 2004. Based on this definition TLS can be classified as clinical or laboratory TLS. Laboratory TLS (LTLS) is characterized by biochemical changes without clinical presentation. Patients can have severe metabolic derangements without clinical symptoms. Clinical TLS (CTLS) is defined as biochemical changes which are accompanied by clinical manifestations and need urgent management [5].

Having increased burden of malignancy and the advancement of therapeutic regimens, it is important to give due attention to the metabolic complications encounter in the highly proliferative HMs, which leads to AKI, cardiac dysrhythmia, seizures and other clinical conditions. These may result in high risk of longer hospital stays, higher cost and death. Since this life-threatening condition may occur rapidly and is preventable, it is crucial to identify patients at risk of developing TLS. Identification of relevant factors predicting TLS is important for the prophylaxis and preventive measures. However, the findings on incidence of LTLS and its factors predicting in patients with HMs is scarce in resource limited-settings such as our country, Ethiopia. Therefore, the aim of this study was to determine the incidence and identify factors predicting LTLS in patients with hematological malignancies [6].

Materials and Methods

Study design and population

A hospital based prospective cohort study was conducted to determine the incidence and identify factors predicting LTLS in adult patients with HMs at Tikur Anbessa Specialized Hospital from September, 2017 to April, 2018. Patients presenting with newly diagnosed HMs and admitted to medical wards or visited hematology unit for chemotherapy treatment and who gave consent during the study period were included in the study. Patients with age less than 15 years were excluded. Study participants received different chemotherapy regimens depending on the type of underlying HMs [7].

Socio-demographic and clinical data collection

Socio-demographic and clinical data were collected using semi-structured data collection forms after getting written informed consent. Socio-demographic data such as age, gender and clinical data concerning prophylaxis, type of malignancy, chemotherapy treatment regimen as well as clinical examination data, including the presence of organomegaly (presence of splenomegaly, hepatomegaly or lymphadenopathy), and preexisting medical conditions like hypertension, Diabetics Mellitus (DM), renal damage, Cardiovascular Disease (CVD), sepsis and Disseminated Intravascular Coagulation (DIC) were collected [8].

Specimen collection and laboratory analysis

The 2ml of venous blood sample with tri-potassium ethylenediamine tetraacetic acid test tube was collected for total WBC count before the initiation of chemotherapy. Additionally, 3ml of venous blood sample was drawn in plain vacutainer test tube to measure the following parameters in all patients before the initiation and daily during chemotherapy. chemotherapy for assessment of LTLS: serum LDH, calcium, phosphate, potassium, and UA. The sample was transported to the national reference laboratory in the Ethiopian Public Health Institute (EPHI) at room temperature within two hours of collection. Total WBC count was analyzed as part of complete blood count using automated analyzer and serum chemistry tests were analyzed by Cobas 6000 automated chemistry analyzer at EPHI. Before laboratory analysis, all the analyzers were checked using quality control materials (e-check control from Sysmex diagnostics and PreciControl ClinChem Multi from Roche Diagnostics) according to the manufacturer's instruction [9].

LTLS definitions

In this study LTLS was assessed, at baseline for spontaneous LTLS and from days 1 to 3 after the initiation of chemotherapy for new onset LTLS, based on the Cairo and Bishop definition criteria using daily measured laboratory values of UA, potassium, phosphate and calcium. UA ≥ 476 µmol/L (8 mg/dL) or 25% increase from baseline, potassium ≥ 6.0 mmol/L (23.5 mg/dL) or 25% increase from baseline, phosphate ≥ 1.45 mmol/L (4.5 mg/dL) or 25% increase from baseline and calcium ≤ 1.75 mmol/L (7 mg/dL) or 25% decrease from baseline were used as a cut-off point to define LTLS. Therefore, LTLS was defined by considering either a 25% increase or decrease from baseline; or level above or below normal, as defined above, for any two or more serum values of UA, potassium, phosphate and calcium reported on the same day. Similarly, spontaneous LTLS (LTLS in the absence of chemotherapy) was defined as a level above or below normal, as defined above, for any two or more serum values of UA, potassium, phosphate and calcium reported on the same day at baseline [10].

Statistical Analysis

The Data was entered into Epi Info 7.2 software and analysis was done with Statistical Package for Social Science (SPSS). Results were presented as absolute numbers with percentages for categorical variables and median with Interquartile Range (IQR) for continuous variables. We performed univariate and multivariate logistic regression analysis to assess the statistical association of factors predicting and the incidence of LTLS. The continuous quantitative variables were transformed into categorical variables for univariate and multivariate analysis. Predicting factors with p-value<0.20 after univariate analysis were entered to multivariate analysis. The results were summarized as the odds ratio with 95% confidence interval and p-value. P value<0.05 was considered as statistically significant [11].

Ethics and consent

Ethical clearance was obtained from University of Gondar, School of Biomedical and Laboratory Science Ethical Committee, and institutional review board in EPHI before the start of sample and data collection. Permission was also taken from Internal Medicine department ethics committee in Tikur Anbessa specialized hospital before enrollment of the patient in the study. The purpose of the study was explained to the study participants and written informed consent was obtained from participants [12].

Results

Baseline socio-demographic and clinical characteristics

Forty nine patients newly diagnosed with HMs were enrolled in our study. Among them, 34 (69.4%) were males and 39 (79.6%) were aged from 15 to 60 years. The median (IQR) age of the patients was 40 (21, 55) years. Most of the patients (71.4%) were diagnosed with leukemia (AML:13, ALL:11 and Chronic Lymphocytic Leukemia (CLL):11) followed by lymphoma (26.5%) (NHL:9 and Hodgkin's lymphoma (HL): 4). Organomegaly was present in 36.7% of patients. All patients received hydration and 40.8% received uric acid lowering agent, allopurinol as TLS prophylaxis treatment (**Table 1**).

Characteristics		Frequency	Percentage
Gender	Female	15	0.306
	Male	34	0.694
Age (years)	15-60	39	0.796
	≥ 60	10	0.204
Underlining malignancy	Leukemia	35	0.714
	Lymphoma	13	0.265
	Multiple myeloma	1	0.02
Organomegaly	Yes	18	0.367
	No	31	0.633
Preexisting medical conditions	Renal damage	1	0.02
	Diabetics mellitus	3	0.061
	Hypertension	2	0.041
	Cardiovascular disease	1	0.02
	Sepsis	3	0.061
	DIC	1	0.02
Hydration prophylaxis	Yes	49	1
	No	-	-
Allopurinol prophylaxis	Yes	20	0.408
	No	29	0.592

DIC: Disseminated intravascular coagulation

Table 1: Socio-demographic and clinical characteristics of study patients.

Incidences of LTLS

The incidence of LTLS was 30.6% (n=15) (95% CI: 18.4-42.9). Spontaneous LTLS occurred in 4.1% (n=2) patients and the incidence of new onset of LTLS was 26.5% (n=13). The incidence of LTLS with respect to the type of HMs were ALL (45.5%), CLL (36.4%), HL (25%), AML (23.1%) and NHL (22.2%). Spontaneous LTLS was observed only in ALL patients [13].

Laboratory abnormalities to define LTLS

The frequent laboratory derangements was hyperuricemia or 25% change from baseline of UA (93.3%) followed by hyperphosphatemia or 25% change from baseline of phosphate (86.7%), hypocalcemia or 25% change from baseline of calcium (26.7%), and hyperkalemia or 25% change from baseline of potassium (6.7%) of all cases of LTLS. The most common laboratory abnormality pair used to define LTLS in this study was hyperuricemia and hyperphosphatemia. About 80.0% of LTLS cases were defined using a pair of deranged UA and phosphate levels followed by pair of UA and calcium (20%), phosphate and calcium levels (6.7%), and paired calcium and potassium derangements (6.7%). There was no change in potassium value that met the criteria for new onset of LTLS [14].

Factors Predicting LTLS

Univariate analysis showed that baseline WBC count ≥ 25x109/L (COR:4.80, 95% CI:1.31-17.66), and LDH level = 2 times the institutional upper limit normal (ULN) (COR:7.00, 95% CI:1.80-27.22) were significantly associated with the development of LTLS. In a multivariate analysis, baseline WBC count = 25x109/L (AOR:5.47, 95% CI:1.11-26.96), and LDH level = 2xULN (AOR:8.97, 95% CI:1.73-46.45) remained significantly associated with LTLS. Although age is not statistically significant in univariate analysis (p value:0.15), age=60 years (AOR: 8.75, 95% CI:1.27-60.56) was also statistically associated with the

development of LTLS in multivariate analysis. Patients with age ≥ 60 years had 8.75 times (AOR:8.75, 95% CI:1.27-60.56) risk of LTLS than age 15-60 years. The risk of LTLS in patients with WBC count ≥ 25x109/L was 5.47 times (AOR:5.47, 95% CI:1.11-26.96) compared to patients with WBC count<25x109/L. Patients with LDH ≥ 2xULN were 8.97 times (AOR:8.97, 95% CI:1.73-46.45) more likely to develop LTLS than patients with LDH<2xULN (**Table 2**)[15].

Variables		LTLS		COR (95% CI)	AOR (95% CI)
		Yes	No		
Gender	Female	4	11	1	-
	Male	11	23	1.32 (0.34-5.08)	
Age	15-60 years	10	29	1	1
	≥ 60 years	5	5	2.90 (0.69-12.15)	8.75 (1.27-60.56)
Baseline WBC count	< 25x109/L	5	24	1	1
	≥ 25x109/L	10	10	4.80 (1.31-17.66)	5.47 (1.11-26.96)
Baseline LDH level	< 2xULN	6	28	1	1
	≥ 2xULN	9	6	7.00 (1.80-27.22)	8.97 (1.73-46.45)
Organomegaly	No	11	20	1	-
	Yes	4	14	0.52 (0.14-1.97)	
Allopurinol prophylaxis	Yes	6	14	1	-
	No	9	20	0.95 (0.28-3.29)	-

LDH: Lactate dehydrogenase, WBC: White blood cell, LTLS: Laboratory tumor lysis syndrome, COR: Crude odds ratio, AOR: Adjusted odds ratio, ULN: Upper limit normal

Table 2: Univariate and multivariate analysis of predictor factors associated with LTLS.

Discussion

In the present study the incidence of LTLS was 30.6%. It is consistent with the incidence of 21.1% reported in the USA. However, our finding is greater than incidence of 11.1% in France, 5% in four European countries and 12 % in Pakistan. On the contrary, the incidence of LTLS in our study is lower compared to 75.5% incidence in Kenya.

The variation may be related to different factors like the difference in TLS prophylaxis, diagnostic definition of TLS, variation of study duration, and stage of the disease at the time of diagnosis or presentation to the health facilities. In our study, allopurinol, a hypouricemic agent was used only for patients with ALL and AML to prevent UA formation. Rasburicase (recombinant urate oxidase) was not used in the current set up of the hospital, which is effective in changing UA into allantoin (rapidly excreted by the kidneys) and recommended for high risk patients. The duration of the study may also affect the incidence of LTLS. Our study does not include patients developing LTLS beyond 3 days of chemotherapy. Regarding the diagnostic definition of TLS, there are no common and consistent diagnostic criteria and previous researches used serum creatinine and LDH to define LTLS in addition to UA, phosphate, calcium and potassium.

The incidence of spontaneous LTLS in the present study was 4.1% and it occurred only in patients with ALL. Moreover, the overall incidence of LTLS was also higher in patients with ALL (45.5%), regardless of the use of allopurinol as prophylaxis. This might be indicative of the highly proliferative rate of tumor cells in ALL and possibly it might be due to delayed presentation to the hospital for chemotherapy treatment.

In this study, baseline WBC count ≥ 25x109/L, LDH level ≥ 2x ULN and age ≥ 60 years were significantly associated with LTLS. This is in agreement with previous studies conducted in patients with different HMs. WBC count and LDH level were found to be indicative of increased burden of malignant cells and were included in the risk assessment for TLS in the previously developed prediction model. High WBC count as a factor predicting LTLS may also be attributable to release of high nucleic acids from intracellular contents of tumor cells which results in an increased UA level. This is indicative of most LTLS cases (80%) in our study were defined by an abnormality pair of UA and phosphate. Patients who are ≥ 60 years of age are 8.75 times more likely to develop LTLS compared to 15-60 years. The possible reason might be due to the decrease in organ function, particularly kidney function as age increases, which are important in the clearing of metabolic products. As age increases, there is a progressive reduction in glomerular filtration rate and renal blood flow.

Small sample size and short follow up period after treatment were the limitation of this study. Monitoring of biochemical parameters was done only once a day. This may result in more likely to miss development of LTLS.

Conclusion

LTLS is a common treatment complication in HMs. Regardless of available preventive measures; more than one-fourth of the patients with HMs undergoing chemotherapy treatments develop LTLS. The highest incidence of LTLS was observed in patients with ALL. Increased baseline WBC count, LDH levels, and age were the independent factors predicting LTLS in patients with HMs.

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