Outcome of tumor lysis syndrome in pediatric patients with hematologic malignancies – a single-center experience from Pakistan

Armaghan-e-Rehman Mansoor,[a] Mohammad Faizan Zahid, MBBS,[a] Mujtaba Mubashir,[a] Zehra Fadoo, MBBS,[b] Anwar ul Haq, MBBS,[c] and Arshalooz Jamila Rahman, MBBS[c]

[a]Medical College, [b]Section of Pediatric Oncology, Department of Oncology, [c]Department of Pediatrics and Child Health, Aga Khan University, Karachi, Pakistan

Background Tumor lysis syndrome (TLS) is serious complication of anticancer chemotherapy, leading to substantial morbidity and mortality in adults and pediatric patients.
Objective To report the incidence and outcomes of TLS in pediatric patients with hematologic malignancies at a center in Pakistan.
Methods Retrospective chart review of 317 pediatric patients with hematologic malignancies during January 2008-December 2013. Demographic features and clinical and laboratory parameters of TLS, with immediate and 6-month outcomes were determined using a semi-structured questionnaire.
Results Median age at diagnosis was 9 years, with the 79.2% patients being male. Laboratory TLS was present in 36 patients (11.4%), with 27 (8.5%) developing clinical TLS and 13 (4.1%) requiring intensive care support. Hyperphosphatemia was the most frequent metabolic abnormality (14.2%), followed by hypocalcemia (13.9%), hyperuricemia (12.6%), and hyperkalemia (1.3%). 45 patients (14.2%) developed acute kidney injury (AKI). Patients who developed TLS had a significantly higher white blood cell count at initiation of chemotherapy (142.0 x 10^9/L [SD, 173.1] vs 31.5 x 10^9/L [SD, 58.0]; $P = .01$) and a higher incidence of AKI (58.3% vs 8.5% of patients; $P < .001$).
Limitations Retrospective design of study, high rate of loss to follow-up, and unavailability of lactate dehydrogenase levels in a majority of patients.
Conclusion The incidence of TLS pediatric hematologic malignancies was 11.4% at our center. The main cause of death was sepsis. Hyperphosphatemia was the common metabolic derangement and hyperkalemia was the least common. TLS warrants intensive supportive care to prevent further morbidity and decrease mortality.

Tumor lysis syndrome (TLS) is a constellation of metabolic derangements manifesting in cancer and other diseases with high cell turnover. In the context of cancer, the onset usually occurs after administration of anti-neoplastic chemotherapy, or it may happen prior to chemotherapy.[1, 2] TLS most commonly occurs with rapidly growing, aggressive malignancies with a high tumor burden, including hematologic malignancies such as acute leukemias and high-grade lymphomas. It may also occur with bulky, solid organ tumors, although this is uncommon in the pediatric population.[3-5]

With the rapid and massive lysis of tumor cells, numerous intracellular ions and compounds are released into the circulation and overwhelm the body's ability to metabolize and excrete these components, thus contributing to the complex pathophysiology of TLS.[4] Hyperkalemia and hyperphosphatemia are caused by the efflux of these ions, which are normally present in high concentrations intracellularly. Hyperkalemia gives rise to cardiac complications, namely arrhythmias, which may prove fatal. Hyperphosphatemia causes hypocalcemia, which in turn adversely affects several organ systems, including the musculoskeletal, cardiovascular, and central and peripheral nervous systems. Hyperuricemia arises from the degradation of nucleic acids released from tumor cells. Formation of uric acid crystals, due to uricosuria, and calcium phosphate crystals within the kidney tubules can cause obstructive uropathy,

Accepted for publication October 23, 2016. Correspondence: Mohammad Faizan Zahid, MBBS; faizanzahid91@hotmail.com. Disclosures The authors report no disclosures or conflicts of interest. JCSO 2016;14(11):457-465. doi: 10.12788/jcso.0300.

impair glomerular filtration rate (GFR) and lead to rapidly declining renal function.[2,6]

The Cairo-Bishop model is currently the most commonly used criteria for the diagnosis of TLS. Laboratory TLS is defined as the presence of least 2 serum metabolic derangements. Clinical TLS comprises laboratory TLS in addition to at least 1 clinical manifestation resulting from the metabolic derangements, such as seizures, arrhythmias, or rising serum creatinine (indicative of renal damage).[7] Under the Cairo-Bishop model, these events must occur either 3 days before or 7 days after initiation of chemotherapy.[7]

TLS is an oncological emergency in both pediatric and adult patients, requiring immediate treatment and supportive care to reduce morbidity and mortality. Acute kidney injury (AKI) and rapidly progressing renal failure with metabolic derangements results in fatal outcomes if not treated promptly.[1,2] The mainstay of therapy for TLS is volume expansion and preserving adequate hydration, and concurrent alkalization of urine may be considered as well.[6] Dialysis may be warranted in cases of severe renal injury and metabolic derangements to provide short-term support for the kidneys.[8] Allopurinol is commonly administered prophylactically before chemotherapy to prevent the formation of uric acid from nucleic acids released from dying tumors cells.[9] Rasburicase, a recombinant urate oxidase, is another approved agent and has demonstrated significant efficacy in not only the treatment but also prevention of TLS. Other forms of urate oxidase, such as uricozyme, may also be used.[10-12] Close observation of clinical condition and laboratory parameters is necessary to optimize treatment and to ensure administration of chemotherapy at optimal doses according to regimen schedule to not compromise treatment efficacy and yield the best possible patient outcomes.[13]

This study outlines the clinical course of 317 pediatric patients with hematologic malignancies treated at The Aga Khan University Hospital, Karachi, Pakistan. The incidence of TLS, the associated metabolic derangements and the outcome of these patients are discussed. To the best of our knowledge, there have been no studies from Pakistan regarding the incidence of TLS and its outcomes among pediatric patients with hematologic malignancies.

Materials and methods

Patient selection and inclusion criteria

During January 2008-December 2013, patients aged under 18 years who presented to the pediatric oncology clinic at the Aga Khan University Hospital, Karachi, Pakistan, with a diagnosis of a hematologic malignancy including acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), Hodgkin lymphoma and Burkitt lymphoma were included in the study. Only chemotherapy-naïve patients were selected for inclusion.

Treatment design and protocols

The induction protocol used in patients with ALL was based on the Berlin-Frankfurt-Munich (BFM) protocol. This includes a 4-drug regimen of vincristine at 1.5 gm/m^2 weekly, oral prednisolone at 60 mg/m^2 daily, L-asparaginase at 2,500 IU/m^2 for 9 doses, and daunomycin at 25 mg/m^2 weekly, with methotrexate on days 1, 15, and 28.[4] For patients with AML, treatment was based on the British Medical Research Council's 10th AML trial (MRC AML 10) protocol, which included cytarabine at 100 mg/m^2 twice daily from days 1-8, daunorubicin at 50 mg/m^2 on days 1, 3, and 5, etoposide at 100 mg/m^2 on days 1-5, and triple intrathecal chemotherapy (methotrexate, hydrocortisone, cytosine arabinoside) on day 1.[14] Patients with Hodgkin lymphoma were treated with alternating cycles of cyclophosphamide, vincristine, prednisone, and procarbazine and adriamycin, bleomycin, vincristine, and dacarbazine. Those with Burkitt lymphoma received therapy according to the FABLMB 96 protocol. This includes cyclophosphamide at 300 mg/m^2 twice a day on days 1-3; adriamycin at 50 mg/m^2 on day 4, vincristine at 1.5 mg/m^2 on days 4 and 11; methotrexate 1,000 mg/m^2 over 24 hours on day 18; cytosine arabinoside 3,000 mg/m^2 twice daily on days 19 and 20; intrathecal methotrexate at 12 mg/m^2 on days 1, 4, 11, and 18; and intrathecal cytarabine at 50 mg/m^2 on days 1, 4, and 11.

Patients were stratified for risk of developing TLS based on the risk-stratification model proposed by Coiffier and colleagues.[6] Prophlactic allopurinol was administered 24-48 hours before chemotherapy to patients who were intermediate and high-risk of developing TLS based on this model.

Patients received intravenous hydration at the rate of 125 ml/ m^2 an hour during TLS. Patients did not receive alkalization therapy. Allopurinol for hyperuricemia was dosed at 400 mg/m^2.

Follow-up protocol included a full history and examination, and laboratory data including complete blood count, serum electrolytes and creatinine. Follow-up was conducted at a median of 6 months after onset of TLS.

Study design

A descriptive, retrospective, review of patient medical records for patients admitted with high-grade hematologic malignancies at The Aga Khan University was conducted during January 2008-December 2013.

Data collection

Patients were identified using the ICD-9 coding by the medical records. Information was noted on a semistructured questionnaire, and consisted of the clinical presentation of the patients and base line laboratory work-up, time lines for presence of initial symptoms, and the time difference of chemotherapy administration and onset of TLS.

Information was also collected on the management strategy for patients with TLS and modifications to chemotherapy and details of any ICU stay were also collected. Lastly, the outcome of these patients was analyzed.

Statistical analysis

Data was analyzed using Statistical Package for Social Sciences 22.0 (SPSS Inc, Chicago, IL, USA). Results were recorded as frequencies, standard deviations, and *P* values. For the purposes of data analysis, a *P* value of .05 was taken as the criterion for statistical significance. Multivariate analysis with binomial logistic regression was performed to assess the association between metabolic abnormalities and AKI.

Ethical consideration

The study and its design were evaluated by the Ethics Review Committee at Aga Khan University Hospital under the protocol number 2973-Ped-ERC-14. No ethical concerns were raised. Any and all information gathered from the patients' confidential medical records for the purpose of this study was kept confidential and disclosed only to the primary investigating team conducting the study.

Results

A total of 317 patients were included in the study, with 251 males and 65 females (Table 1). ALL was the most frequent underlying malignancy (64.0%) while Burkitt lymphoma was the least frequent (6.6%). The mean age of the patients at diagnosis was 9.2 years (SD, 5.4 years), with a median age of 9 years (range, 6 months to 18 years). The mean duration between diagnosis and the administration of chemotherapy was 3.2 days (SD, 3.8), with a median duration of 2 days.

Of all the patients included in this study, 36 (11.4%) developed laboratory TLS based on the Cairo-Bishop model criteria. Hyperphosphatemia was the most common metabolic derangement, observed in 45 (14.2%) patients. Hyperkalemia was the least common problem, observed in 4 (1.3%) patients. Of the patients who developed laboratory TLS, 20 (55.6%) had 2 metabolic derangements, 14 (38.9%) had 3, and 2 (5.6%) had 4, as outlined in the criteria for diagnosing TLS. The mean duration between the initiation of chemotherapy and the development of laboratory TLS was 1.1 days (SD, 1.1), with a median of <1 day (range, <1-4 days). Based on the stratification for TLS risk, 246 (87.2%) patients received prophylactic allopurinol. All of the 36 patients developing TLS belonged to this group. None of the patients developed side effects related to TLS prophylaxis.

AKI was seen in 45 (14.2%) of all patients admitted for chemotherapy, with stage 1 AKI being the most frequently seen in 36 patients (11.4%). Details about TLS, AKI, and metabolic derangements are given in (Table 1).

TABLE 1 Basic and biochemical characteristics in the study population

Characteristic	n (%)
Mean age, y (SD)[median]: 9.2 (5.4) [9]	—
Sex	
Male	251 (79.2)
Female	65 (20.5)
Malignancy	
ALL	203 (64.0)
AML	58 (18.3)
Hodgkin lymphoma	35 (11.0)
Burkitt lymphoma	21 (6.6)
AKI	
No AKI	272 (85.8)
Stage 1	36 (11.4)
Stage 2	7 (2.2)
Stage 3	2 (0.6)
Laboratory TLS	
Yes	36 (11.4)
No	281 (88.6)
Metabolic derangements	
Hyperkalemia	4 (1.3)
Hyperphosphatemia	45 (14.2)
Hyperuricemia	40 (12.6)
Hypocalcemia	44 (13.9)
Mean time diagnosis to chemotherapy, d (SD) median]: 3.2 (3.8) [2]	—
Mean time chemotherapy to TLS, d (SD) [median]: 1.1 (1.1) [<1]	—

ALL, acute lymphoblastic leukemia; AKI, acute kidney injury; AML, acute myeloid leukemia; BC, white blood cell; CNS, central nervous system; LDH, lactate dehydrogenase; TLS, tumor lysis syndrome

TLS was diagnosed in 27 (75%) of the 36 patients who developed laboratory TLS. AKI was the only clinical sign that fulfilled the criteria for the diagnosis of clinical TLS in all 27 patients (Table 2). All of the patients received IV hydration to correct the AKI. Allopurinol was used to manage 33 patients (91.7%). Two patients with TLS required delay in chemotherapy and resumption at a later date because they had febrile neutropenia. None of the patients required reduction in the dose of primary chemotherapy for their respective cancers.

TABLE 2 Outcomes of tumor lysis syndrome in 36 patients

Characteristic	n (%)
Clinical TLS	
Present	27 (75)
Absent	9 (25)
Presenting sign for clinical TLS	
AKI (creatinine, >1.5 ULN)	27 (100)
Arrhythmias	0
Sudden death	0
Seizure	0
Management of TLS	
IV hydration	36 (100)
Allopurinol	33 (91.7)
Chemotherapy withdrawal	2 (5.6)
Dialysis	1 (2.8)
No. of metabolic merangements on laboratory TLS criteria	
2	20 (55.6)
3	14 (38.9)
4	2 (5.6)
ICU admission	
No. patients admitted	13 (36.1)
Reason for ICU admission	
Close monitoring for TLS	7 (53.8)
Sepsis	1 (7.7)
Acute respiratory failure	2 (15.4)
Management of AKI	3 (23.1)
Mean length of stay, d (SD) [median]: 4.3 (3.2) [3]	—
Final outcome	
Alive with complete remission	7 (19.4)
Alive with refractory disease	5 (13.9)
Alive with relapse	5 (13.9)
Death during same admission (when TLS occurred)	3 (8.3)
Death later	4 (11.1)
Lost to follow-up	12 (33.3)

AKI, acute kidney injury; ICU, intensive care unit; TLS, tumor lysis syndrome

One patient with TLS required dialysis for severely high creatinine levels, hyperphosphatemia, hypocalcemia, and hyperuricemia. In all, 13 patients (36.1%) required ICU admission, with 7 of those admitted to the ICU initially for close monitoring for TLS alone, 2 for acute respiratory failure, 3 for AKI, and 1 for sepsis. The mean length of ICU stay was 4.3 days (SD, 3.2), with a median stay of 3 days.

A comparison of demographic factors and clinical parameters between patients developing laboratory TLS and those who did not develop laboratory TLS was performed (Table 3). Patients with Burkitt lymphoma were more likely to develop TLS than were patients with acute leukemias. None of the patients with Hodgkin lymphoma developed TLS during chemotherapy. Patients who developed TLS had a higher mean white blood cell (WBC) count at the start of chemotherapy, with a shorter time interval between diagnosis and the initiation of chemotherapy. Patient age was not a significant determinant of the development of TLS ($P = .967$).

Presence of TLS was strongly associated with AKI, with 21 patients (58.3%) with TLS having an episode of AKI, while only 24 (8.5%) of those without laboratory TLS developed AKI ($P < .001$). Univariate analysis showed that all 4 metabolic derangements in TLS had a statistically significant correlation with AKI (P values of less than .05). These were entered into a binomial logistic regression model as multivariate analysis. Multivariate analysis showed hyperphosphatemia and hyperuricemia as independent laboratory parameters significantly associated with the development of AKI, whereas hypocalcemia and hyperkalemia were no longer significant (Table 4).

At a median follow-up of 6 months, 17 of 36 patients with TLS were alive. None of those patients had any residual evidence of kidney injury or metabolic derangements. Three patients (8.3%) died during the same hospital admission (when TLS occurred), with the cause of death reported as sepsis secondary to fungal infection in 2 patients, and sepsis secondary to vancomycin-resistant *Enterococci* and Staphylococcal infection in the third patient. Four patients (11.1%) died later in the course of their illness. Three of those four patients died from sepsis secondary to fungal infection, and 1 patient died of hypovolemic shock due to severe gastroenteritis. Twelve patients (33.3%) were lost to follow-up (Table 2).

Discussion

The most commonly occurring malignancies in the pediatric age group include leukemias (25%), lymphomas (both Hodgkin and non-Hodgkin; 23%), and primary brain tumors (17%).[15] Considering that TLS usually occurs in fast-growing and aggressive cancers, it is not surprising that pediatric patients are at a considerable risk of developing TLS during the course of treatment.[4] The reported incidence of TLS in cancer patients varies from study to study, depending on several factors such as the type of malignancy studied, treatment protocols, sample size, patient populations, and the methodology applied. Most published studies describing TLS involve patients with hematologic malignancies.[4] Collectively, an approximate incidence of TLS in pediatric patients with acute leukemias is reported

TABLE 3 Comparison of patient characteristics between patients with and without laboratory tumor lysis syndrome

Characteristic	Tumor lysis syndrome		*P* value
	Present	Absent	
Sex, n (%)			.491
Male	26 (72.2)	225 (80.1)	
Female	10 (27.8)	56 (19.9)	
Acute kidney injury, n (%)			<.001
Yes	21 (58.3)	24 (8.5)	
No	15 (41.7)	257 (91.5)	
Malignancy, n (%)			<.001
Acute leukemias			
AML	3 (5.2)	55 (94.8)	
ALL	26 (12.8)	177 (87.2)	
Burkitt lymphoma	7 (33.3)	14 (66.7)	
Hodgkin lymphoma	0 (0)	35 (100)	
Mean age at diagnosis, y [SD]	8.6 [5.1]	9.3 [5.4]	.967
Mean time from diagnosis to initiation of chemotx, d [SD]	2.0 [2.2]	3.4 [3.9]	.010
Mean WBC count at start of chemotx, x10^9 cells/L [SD]	142.0 [173.1]	31.5 [58.0]	.001

ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; chemotx, chemotherapy; TLS, tumor lysis syndrome; WBC, white blood cells

TABLE 4 Multivariate analysis correlating the risk of acute kidney injury with metabolic derangements

Metabolic derangement	Acute kidney injury, n (%)		OR (95% CI)	*P* value
	Present	Absent		
Hyperkalemia			0.64 (0.05-7.78)	.728
Yes	2 (4.4)	2 (0.7)		
No	43 (93.6)	270 (99.3)		
Hyperphosphatemia			6.36 (2.78-14.58)	<.001
Yes	23 (51.1)	22 (8.1)		
No	22 (48.9)	250 (91.9)		
Hyperuricemia			4.32 (1.60-11.67)	.004
Yes	21 (46.7)	19 (7.0)		
No	24 (53.3)	253 (93.0)		
Hypocalcemia			2.25 (0.85-6.00)	.104
Yes	20 (44.4)	24 (8.8)		
No	25 (55.6)	248 (91.2)		

CI, confidence interval; OR, odds ratio

to be 3%-7%, whereas the incidence for high-grade lymphomas is 4%-11%.[4,16,17]

The cumulative incidence of TLS in our study was 11.4%, with 8.5% of patients fulfilling the criteria for clinical TLS. In comparison, a study by Bagshi and colleagues,[18] reported a TLS incidence of 19% in children with ALL. Alavi and colleagues reported a TLS incidence of 11.85% for children with non-Hodgkin lymphoma.[19] Although these incidence rates are comparable with our results, some studies have reported substantially higher incidence rates. For example,

a case review conducted on patients with intermediate to high-grade non-Hodgkin lymphoma (NHL) found an incidence of 42% for TLS,[20] and another study reported an even greater incidence of 70%.[21] These and several other studies report the outcome of TLS in patients with hematologic malignancies (Table 5).[22, 21, 23]

A large, multicenter, population-based cohort study reported that the incidence of AKI in lymphoma and leukemia were 28.1% and 37.9%, respectively.[18] A study by Darmon and colleagues found that the incidence of AKI in high-grade hematologic malignancies with TLS was as high as 63.8%, whereas AKI in the absence of TLS was 18.9%.[24] In a previous study from our center involving 365 adult patients with lymphoma, Khalil and colleagues reported that AKI occurring in 31.8% of the patients.[25] Detailed analysis showed that 18 of 28 patients (64.3%) who developed TLS had developed AKI. Another study showed an AKI incidence of 57.1% in patients with NHL developing TLS, whereas incidence of AKI in the non-TLS group was 24.4%.[19] These large variations in the incidence of AKI in TLS may be attributable to differences in hospital protocols and management guidelines according

TABLE 5 Representative studies reporting the outcome of tumor lysis syndrome in patients with hematologic malignancies

Author	Type of malignancy	N	Development of TLS			Therapeutic, preventive measures	TLS-related mortality, n (%)	Risk factors for TLS
			Laboratory	Clinical	n (%)			
Zhang[22]	AML, ALL	380	77	2	79 (20.8)	Hydration, allopurinol, urine alkalinization	NR	High WBC count, male gender, lymphomatous presentation (lymphadeno- pathy, splenomegaly), elevated AST, pretreatment for renal insufficiency, pre- treatment for hyperuricemia, elevated serum LDH
Hande[20]	High and intermediate grade NHL	102	43	6	49 (48)	Hydration, allopurinol, urine alkalinization	0	Pretreatment renal insufficiency
Al Bagshi18	ALL	398	69	5	74 (19)	Hydration, allopurinol, urine alkalinization	0	High WBC count, lymphomatous presentation (lymphadenopathy, spleno- megaly), elevated serum LDH, CNS involvement, male sex
Alavi[19]	Burkitt lymphoma, lymphoblastic lymphoma, anaplastic large-cell lymphoma	59	7	7	14 (23.7)	Hydration, allopurinol, urine alkalinization	3 (21.4)	None identified
Kedar[21]	ALL, AML	30	20	1	21 (70)	Hydration, allopurinol, urine alkalinization	NR	None identified
Ahn[29]	AML, ALL, NHL	396	32	36	68 (17.2)	Hydration, allopurinol, urine alkalinization; rasburicase in 10.9% of the cases	NR	Burkitt lymphoma, ALL, pretreatment renal insufficiency, pretreatment hyper-uricemia, high WBC count, elevated serum LDH, hypophosphatemia
Abdel-Baset[23]	ALL	60	Not mentioned	Not mentioned	27 (45)	Not elaborated	0	High WBC count, lymphomatous presentation, T-cell phenotype, elevated serum LDH, male gender, age ≥10 y

ALL, : acute lymphoblastic leukemia; AML, acute myeloid leukemia; AST, aspartate aminotransferase; CNS, central nervous system; LDH, lactate dehydrogenase; NHL, non-Hodgkin lymphoma; WBC, white blood cells

to center and country, such as the use of allopurinol, availability of rasburicase and other urate oxidase formulations and frequency of monitoring for electrolytes during admission. The incidence of AKI associated with TLS in our study was 14.2%, which is much lower than that reported in some of the studies discussed above.

We observed hyperphosphatemia and hyperuricemia to be significantly associated with AKI. Hyperphosphatemia has been shown to promote the formation of calcium phosphate crystals, thereby increasing the risk of AKI.[26] Similarly, hyperuricemia can cause AKI by precipitating urate stone formation, and may cause additional injury by reducing renal perfusion and promoting inflammation.[27]

A number of factors influence the risk and severity of TLS in cancer patients. Such factors include the type of malignancy, the rate of associated cell turnover, sensitivity to chemotherapy, and the type and intensity of chemotherapy.[4] Patients with volume depletion, decreased urinary flow, pre-existing hyperuricemia and kidney disease are at increased risk as well.[20,28] Some studies have demonstrated an increased likelihood of TLS in male patients with hematologic malignancies,[22,18,23] however, our results showed no relationship between gender and TLS risk. CNS involvement and lymphomatous presentation (like in the case of AML and ALL) correlate with a higher tumor burden and aggressive tumor biology and are associated with an increased risk of developing TLS.[23,22,18] Another risk factor identified is hypophosphatemia, which is a novel finding.[29] It is plausible to attribute low serum phosphate levels to consumption by rapidly developing tumor cells for the synthesis cellular components. This would result in a shift of serum phosphate into the intracellular compartment, giving rise to hypophosphatemia, as has been observed with ALL and Burkitt lymphoma.[30] The best management for TLS is prevention by administering risk tailored prophylactic measures, especially in patients who have a higher likelihood of developing TLS, based on the risk factors we discussed above.

An increased incidence of TLS has also been reported with certain chemotherapy regimens, especially those containing specific drugs such as cytarabine, etoposide, and corticosteroids. This holds true especially for lymphoid malignancies, because such drugs are highly lympholytic and result in rapid and widespread lysis of malignant lymphoid cells. Although TLS has been reported to occur before starting chemotherapy,[1,2] none of our patients developed TLS before chemotherapy.

Burkitt lymphoma and ALL are most frequently associated with TLS.[17, 31, 32] These malignancies are highly chemosensitive and often present with large cumulative mass of tumor cells at the time of diagnosis and chemotherapy, resulting in massive and rapid lysis of tumor cells. This particularly places patients with ALL and Burkitt lymphoma at a high risk for developing TLS.[4,33] In our study, the greatest incidence of TLS was among patients with Burkitt lymphoma (33.3%), followed by patients with ALL (12.8%). In fact, we observed a significantly increased risk of TLS in patients with Burkitt lymphoma in comparison to those with acute leukemias.

High WBC count is indicative of a larger tumor cell mass and hence can be used to gauge the risk of TLS before chemotherapy.[34] In our study, WBC counts at the start of chemotherapy were significantly higher for patients developing TLS in comparison to those not developing TLS. Patients developing TLS in our study had a lower mean duration of time between diagnosis and initiation of chemotherapy. This might have been, in part, due to the urgency with which their chemotherapy was started, based on significantly abnormal laboratory results and worse signs and symptoms compared with patients with low-grade malignancies, and may not likely represent a causal relationship. Based on such observations, Coiffer and colleagues proposed a risk stratification model that incorporated WBC count, type of malignancy, and choice of treatment.[6] This is a viable algorithm for the stratification of patients at risk for pre-emptive prophylaxis and therapeutic measures to reduce the incidence of and the morbidity and mortality associated with TLS.

Supportive care should focus on maintaining adequate hydration and correcting metabolic derangements. Volume expansion and preserving adequate hydration form the backbone of prevention of TLS in high-risk patients and plays a fundamental role as primary supportive therapy after the development of TLS. Profound derangements and rapidly declining renal function should prompt the need for dialysis, as was the case with one of the patients in our study and another patient in the study by Hande and colleagues.[20]

One adjunctive method to treat and prevent hyperuricemia during TLS is to block its production during catabolism of nucleic acids released from malignant cells. Allopurinol is an inhibitor of xanthine oxidase, responsible for converting metabolites of purine degradation (hypoxanthine and xanthine) to uric acid.[35] Allopurinol has demonstrated great efficacy in preventing the formation of uric acid and dramatically reduce the incidence of obstructive urate nephropathy in cancer patients at high risk for developing TLS.[10] However, blocking of xanthine oxidase leads to the increased serum levels of xanthine and hypoxanthine, increasing the inherent risk of these metabolites precipitating in renal tubules, forming calculi, and causing obstructive uropathy.[7,36,37]

Rasburicase, a recombinant urate oxidase that converts uric acid to the more soluble compound allantoin, is another approved agent in the US and Europe for the treatment and prevention of TLS.[12] It has been shown to significantly decrease the incidence of TLS when used prophylactically in pediatric patients as well as to correct hyperuricemia

when administered therapeutically.[12] The role of allopurinol is currently being phased out in favor of rasburicase, because allopurinol has been shown to be comparatively less effective in prophylactic treatment and for management of TLS, and is also associated with more potential side effects.[10] However, because of its high cost, rasburicase is not readily available at hospitals across Pakistan, and hence was not used in the management of patients in this study.[38] The promising role of rasburicase in not only preventing but also treating TLS should prompt local health policy and governing bodies to implement a system for its availability in the country.

The solubility of products of purine degradation varies and is dependent on urinary pH. Thus, alkalinization of urine is a commonly used method to increase the solubility of uric acid and thereby increasing its elimination.[6] However, alkalinization carries an inherent risk of producing metabolic alkalosis, especially in patients with AKI and reduced GFR, which can lead to further deterioration. In addition, increased urinary pH increases the risk of formation of calcium phosphate, xanthine, and hypoxanthine calculi, which can also lead to obstructive uropathy.[6] These limitations and associated risks have led experts to question the use of alkalinization of urine in TLS, thus its routine use is gradually becoming controversial.

ICU admission was required for 13 patients (36.1%) with TLS in our study. Although this is a high rate, 7 of those patients were shifted to the ICU only for close monitoring of TLS, and had no clinical manifestations. We believe it reflects a cautionary approach in our institutional setting in an attempt to preemptively treat any accompanying complications to reduce morbid outcomes. This strategy is in line with recommendations put forward by experts in the management of patients at high risk of developing TLS and those already developing TLS with clinical manifestations.[4]

During the course of TLS, we observed a mortality rate of 8.3%, with infections being the cause of death. Subsequently, 11.1% of patients died after discharge, during the course of illness, most commonly secondary to systemic mycosis. These figures are comparable with outcomes reported in a trial conducted by the International NHL-Berlin-Frankfurt-Münster group, which showed an overall mortality of 11% was observed in the 63 patients developing TLS, with 2 patients subsequently dying of electrolytes imbalances.[39]

To the best of our knowledge, this is the first study investigating the incidence, risk factors, and outcomes of TLS among pediatric patients with hematologic malignancies from Pakistan. The strengths of our study include robust inclusion criteria, with exclusion of patients with prior kidney disease, and a thorough review of patient outcomes and management. However, the retrospective design of our study is a limitation, as is the high rate of loss to follow-up and unavailability of lactate dehydrogenase levels in a majority of patients.

To conclude, TLS is a common complication during treatment of children with hematologic malignancies. Burkitt lymphoma and ALL are the most commonly associated with TLS. In the present study, the incidence of laboratory TLS was found in 11.4% of patients, and clinical TLS in 8.5%. Of those patients, 36.1% required ICU admission. The mortality rate observed was 8.3%. Development of TLS was associated with a high WBC count at initiation of chemotherapy. This data can be used to modify existing protocols for TLS management and prevention to decrease the morbidity and mortality associated with the complication. Guidelines can be developed from this information to see if certain parameters should be monitored more aggressively to detect and prevent development of TLS and AKI in patients receiving chemotherapy.

References

1. Wilson FP, Berns JS. Onco-nephrology: tumor lysis syndrome. Clin J Am Soc Nephrol. 2012;7:1730-1739.
2. Abu-Alfa AK, Younes A. Tumor lysis syndrome and acute kidney injury: evaluation, prevention, and management. Am J Kidney Dis. 2010;55(suppl 3):S1-S13.
3. Baeksgaard L, Sørensen J. Acute tumor lysis syndrome in solid tumors – a case report and review of the literature. Cancer Chemother Pharmacol. 2003;51:187-192.
4. Chang JE, Medlin SC, Kahl BS, et al. Augmented and standard Berlin-Frankfurt-Münster chemotherapy for treatment of adult acute lymphoblastic leukemia. Leuk Lymphoma. 2008;49:2298-2307.
5. Mirrakhimov AE, Voore P, Khan M, et al. Tumor lysis syndrome: a clinical review. World J Crit Care Med. 2015;4:130-138.
6. Coiffier B, Altman A, Pui C-H, et al. Guidelines for the management of pediatric and adult tumor lysis syndrome: an evidence-based review. J Clin Oncol. 2008;26:2767-2778.
7. Cairo MS, Bishop M. Tumour lysis syndrome: new therapeutic strategies and classification. Br J Hematol. 2004;127:3-11.
8. Conger JD, Falk SA. Intrarenal dynamics in the pathogenesis and prevention of acute urate nephropathy. J Clin Invest. 1977;59:786-793.
9. Smalley RV, Guaspari A, Haase-Statz S, et al. Allopurinol: intravenous use for prevention and treatment of hyperuricemia. J Clin Oncol. 2000;18:1758-1763.
10. Goldman SC, Holcenberg JS, Finklestein JZ, et al. A randomized comparison between rasburicase and allopurinol in children with lymphoma or leukemia at high risk for tumor lysis. Blood. 2001;97:2998-3003.
11. Patte C, Sakiroglu C, Ansoborlo S, et al. Urate-oxidase in the prevention and treatment of metabolic complications in patients with B-cell lymphoma and leukemia, treated in the Societe Francaise d'Oncologie Pediatrique LMB89 protocol. Ann Oncol. 2002;13:789-795.
12. Ho VQ, Wetzstein GA, Patterson SG, et al. Abbreviated rasburicase dosing for the prevention and treatment of hyperuricemia in adults at risk for tumor lysis syndrome. Support Cancer Ther. 2006;3:178-182.
13. Howard SC, Jones DP, Pui C-H. The tumor lysis syndrome. New England Journal of Medicine 2011;364:1844-54.
14. Riley LC, Hann IM, Wheatley K, et al. Treatment-related deaths during induction and first remission of acute myeloid leukaemia

in children treated on the Tenth Medical Research Council Acute Myeloid Leukaemia Trial (MRC AML10). British journal of haematology 1999;106:436-44.
15. Kobayashi D, Wofford MM, McLean TW, et al. Spontaneous tumor lysis syndrome in a child with T-cell acute lymphoblastic leukemia. Pediatric blood & cancer 2010;54:773-5.
16. Annemans L, Moeremans K, Lamotte M, et al. Incidence, medical resource utilisation and costs of hyperuricemia and tumour lysis syndrome in patients with acute leukaemia and non-Hodgkin's lymphoma in four European countries. Leuk Lymphoma. 2003;44:77-83.
17. Wössmann W, Schrappe M, Meyer U, et al. Incidence of tumor lysis syndrome in children with advanced stage Burkitt lymphoma/leukemia before and after introduction of prophylactic use of urate oxidase. Ann Hematol. 2003;82:160-165.
18. Al Bagshi M, Sadek A, Hassan E, et al. Tumor lysis syndrome in children with acute leukemia: incidence and outcome. J Appl Hematol. 2013;4:100-103.
19. Alavi S, Arzanian MT, Abbasian MR, et al. Tumor lysis syndrome in children with non-Hodgkin lymphoma. Ped Hematol Oncol. 2006;23:65-70.
20. Hande KR, Garrow GC. Acute tumor lysis syndrome in patients with high-grade non-Hodgkin's lymphoma. Am J Med. 1993;94:133-139.
21. Kedar A, Grow W, Neiberger RE. Clinical versus laboratory tumor lysis syndrome in children with acute leukemia. Ped Hematol Oncol. 1995;12:129-134.
22. Zhang Q, Liu KQ, Liu BC, et al. [Analysis of tumor lysis syndrome in 380 cases of acute leukemia]. Zhongguo Shi Yan Xue Ye Xue Za Zhi. 2015;23:61-64.
23. Abdel-Baset HA, Eldin EN, Eltayeb AA, et al. Clinical and laboratory approach for the identification of the risk for tumour lysis syndrome in children with acute lymphoblastic leukemia. Life Sc J. 2012;9(1):189-195.
24. Darmon M, Vincent F, Camous L, et al. Tumour lysis syndrome and acute kidney injury in high-risk haematology patients in the rasburicase era. A prospective multicentre study from the Groupe de Recherche en Réanimation Respiratoire et Onco-Hématologique. Br J Haematol. 2013;162:489-497.
25. Khalil MAM, Latif H, Rehman A, et al. Acute kidney injury in lymphoma: a single centre experience. https://www.hindawi.com/journals/ijn/2014/272961/. Int J Nephrol. Published February 3, 2014. Accessed November 5, 2016.
26. Howard SC, Ribeiro RC, Pui C-H. Acute complications. Ching-Hon Pui, ed. In: Childhood leukemias (3rd ed). Cambridge, United Kingdom: Cambridge University Press; 2012; pp 660-700.
27. Ejaz AA, Mu W, Kang DH, et al. Could uric acid have a role in acute renal failure? Clin J Am Soc Nephrol. 2007;2:16-21.
28. Tsokos GC, Balow JE, Spiegel RJ, et al. Renal and metabolic complications of undifferentiated and lymphoblastic lymphomas. Medicine (Baltimore). 1981;60:218-229.
29. Ahn YH, Kang HJ, Shin HY, et al. Tumour lysis syndrome in children: experience of last decade. Hematol Oncol. 2011;29:196-201.
30. Wollner A, Shalit M, Brezis M. Tumor genesis syndrome. Hypophosphatemia accompanying Burkitt lymphoma cell leukemia. Miner Electrolyte Metab. 985;12:173-175.
31. Jabr FI. Acute tumor lysis syndrome induced by rituximab in diffuse large B-cell lymphoma. Int J Hematol. 2005;82:312-314.
32. Jeha S. Tumor lysis syndrome. Semin Hematol. 2001;38(4 suppl 10):4-8.
33. Stapleton FB, Strother DR, Roy S, et al. Acute renal failure at onset of therapy for advanced stage Burkitt lymphoma and B cell acute lymphoblastic lymphoma. Pediatrics. 1988;82:863-869.
34. Knoebel RW, Lo M, Crank CW. Evaluation of a low, weight-based dose of rasburicase in adult patients for the treatment or prophylaxis of tumor lysis syndrome. J Oncol Pharm Pract. 2011;17:147-154.
35. Krakoff IH, Meyer RL. Prevention of hyperuricemia in leukemia and lymphoma: use of allopurinol, a xanthine oxidase inhibitor. JAMA. 1965;193:1-6.
36. Ogawa A, Watanabe K, Minejima N. Renal xanthine stone in Lesch-Nyhan syndrome treated with allopurinol. Urology. 1985;26:56-58.
37. Spector T. Inhibition of urate production by allopurinol. Biochem Pharmacol. 1977;26:355-358.
38. Reinders M, van Roon E, Brouwers J, et al. A costly therapeutic dilemma in tophaceous gout: is etanercept or rasburicase preferable? Ann Rheumatic Dis. 2005;64:516.
39. Seidemann K, Meyer U, Jansen P, et al. Impaired renal function and tumor lysis syndrome in pediatric patients with non-Hodgkin's lymphoma and B-ALL. Observations from the BFM-trials. Klin Padiat. 1997;210:279-284.