East African Medical Journal Vol. 84 No. 3 March 2007
INCIDENCE OF CHEMOTHERAPY-RELATED TUMOUR LYSIS SYNDROME AT KENYATTA NATIONAL HOSPITAL, NAIROBI
W. Busakhala, MBChB, Senior House Officer, Department of Medicine, M.D. Joshi, MBChB, MMed, MPH, FACC, Senior Lecturer and Director, Clinical Epidemiology Unit, Department of Medicine, N.O. Abinya, MBChB, MMed, Associate Professor and Consultant Physician and Haemato-oncologist, Department of Medicine, A. Amayo, MBChB, MMed, Senior Lecturer and Consultant Pathologist, Department of Chemical Pathology, College of Health Sciences, University of Nairobi, P.O. Box 30197-00100, Nairobi, Kenya and H.O. Abwao, MBChB, DMRT, MRCR, Chief Specialist and Head, Cancer Treatment Centre, Kenyatta National Hospital, P.O. Box 20723, Nairobi, Kenya

Request for reprints to: Dr. M.D. Joshi, Department of Medicine and Clinical Epidemiology Unit, College of Health Sciences, University of Nairobi, P.O. Box 30197-00100, Nairobi, Kenya

INCIDENCE OF CHEMOTHERAPY-RELATED TUMOUR LYSIS SYNDROME AT KENYATTA NATIONAL HOSPITAL, NAIROBI

W. BUSAKHALA, M.D. JOSHI, N.O. ABINYA, A. AMAYO and H.O. ABWAO

ABSTRACT

Objectives: **To estimate the magnitude of laboratory defined Tumour Lysis Syndrome (TLS) at Kenyatta National Hospital (KNH), identify its pattern of presentation, resolution, and determine the biochemical outcome of affected patients.**

Design: **Prospective patient-treatment cohort study.**

Setting: **Kenyatta National Referral and Teaching Hospital, between November 2004 and April 2005.**

Subjects: **One hundred and forty two patients receiving first course chemotherapy.**

Main Outcome measure: **Laboratory defined Tumour Lysis Syndrome (TLS).**

Results: **One hundred and eleven patients completed the study protocol. Forty two patients (37.8%) developed TLS. The incidence in haematological malignancies was 75.5% while in non-haematological malignancies was 3.6%. Hyperphosphataemia and hyperkalaemia were the most consistent diagnostic parameters while hyperuricaemia occurred in only one patient. No patient developed hypocalcaemia. Ninety five percent of patients developed TLS within the first three days of receiving chemotherapy while 55% resolved in the first week. Two TLS case mortalities occurred.**

Conclusions: **The incidence of TLS in this cohort study was 38%, and was highest among haematological malignancies. No cases occurred in breast cancer patients. Majority of the cases were diagnosed on the basis of increase in serum phosphate and potassium; uric acid did not rise predominantly due to prophylactic uricosuric therapy. A majority (95%) developed within three days of commencing chemotherapy.**

INTRODUCTION

Tumour Lysis Syndrome (TLS) refers to a group of biochemical changes that occur following rapid death or cytolysis of malignant cells with release of intracellular components to the extra-cellular environment. The main biochemical changes involve increase in serum phosphate, potassium, uric acid and decline in serum calcium. In some of the patients, the biochemical changes can manifest clinically as renal, cardiac, muscle and neuronal dysfunction. Cytolysis of tumour cells can be caused by chemotherapy, radiotherapy, or it can occur spontaneously (1).

There are two types of chemotherapy-related TLS as defined by Hande and Garrow in 1993 (1).

Laboratory TLS refers to a minimum of two of the following metabolic changes occurring within four days of initiating chemotherapy: a 25% increase in serum phosphate, potassium and uric acid or a 25% decline in the serum calcium concentration. Clinical TLS is defined as laboratory TLS plus one of the following; renal failure, cardiac arrhythmias or sudden death (1).

In addition, high serum levels of lactate dehydrogenase (LDH) >1500 U/L, disseminated intravascular coagulation and fever may develop (2). Thus TLS may easily pass for infection or bone marrow suppression, which are two of the most common complications of chemotherapy (3). Sometimes it can occur concurrently with bone marrow suppression and infection with fatal consequences (4).

Laboratory TLS has been found to occur in 70% of leukaemia's and lymphomas although less than 6% manifest clinically (1). Prevention and early detection are the most important and effective interventions. However, the reliance on clinical manifestations to diagnose TLS has led to under reporting because about 94% of patients developing TLS are asymptomatic (1).

Identification of locally relevant diagnostic markers and clinical predictors of TLS are a prerequisite in the prophylaxis, diagnosis and treatment of a condition with potentially significant morbidity and mortality. In Africa in general and Kenya in particular, studies on TLS are lacking. Thus in this hospital-based observational prospective study we aimed to establish incidence and clinical factors associated with development of TLS and hence bridge the existing knowledge gap.

MATERIALS AND METHODS

A prospective cohort study design was conducted at the KNH, a tertiary national referral centre, between November 2004 and April 2005. Consecutive patients were screened and recruited from Oncology, Medical and Gynaecology wards and haematology-Oncology, and Radiotherapy clinics. Inclusion criteria consisted of aged: 13 years and above, chart documented tissue diagnosis of cancer receiving first course of chemotherapy, with a minimum glomerular filtration rate (GFR) of 90mls/min/1.73m2. Exclusion criteria included: patients receiving uricosuric agents for indications other than TLS, post-renal transplant patients, moderate and severelly dehydrated patients, those unwilling to come back to the hospital for four consecutive days and failure to consent. Patients declining consent, were characterised by age, gender and tumour type.

The decision to start chemotherapy was entirely at the discretion of the primary care clinician as per the KNH treatment protocols, and was not investigators influenced. Patients receiving chemotherapy were consecutively recruited. The principal investigator took history to document bio-data, functional status and examined patients to document weight, height, hydration status and overall clinical state. Recruited patients underwent pretreatment evaluation for plasma uric acid, urea, creatinine, potassium, uric acid, phosphate and calcium on day zero, as part of baseline evaluation. On initiation of chemotherapy, these laboratory tests and clinical evaluation were repeated at 24-hour intervals for four days. Patients who developed laboratory TLS had tests repeated on day seven to document biochemical resolution, failing which further testing was carried out on day 15. This study adapted the Hande and Garrow definition of laboratory TLS as had been widely used in other published studies (1,5,6).

Uric acid, phosphates, calcium, BUN, and creatinine were analysed utilising Olympus AU400 automated clinical chemistry analyser (7) and a calculated GFR was derived. Calcium was corrected for serum albumin using a standard formula (8). The procedures of specimen collection and preparation were followed strictly to minimise pre-analytical sources of error. Before analysis, all the assays were calibrated according to the manufacturer's specifications and three levels of control (high, medium and low) were used to validate the calibration. The results were only accepted if the controls were within the accepted limits (9).

RESULTS

Medical records of 366 patients with a tissue diagnosis of cancer were screened; 158 were excluded on basis of receiving radiotherapy; 21 on account of a GFR of less then 90 mls/hr and 45 patients for being unwilling to return to the hospital for four consecutive days. Excluded patients mirrored recruited patients in terms of gender, age and tumour type; cancer type distribution in excluded patients were: breast cancer (BRCA) 42%, Non-Hodkins lymphoma (NHL) 16% and chronic

leukaemia's 14%; male female ratio of 1:2 and age distribution is depicted in Figure 1.

Thirty one patients were excluded from the analysis on account of chemotherapy protocol interruption; for reason of drug unavailability or loss to follow up. Thus complete data were available for one hundred and eleven patients. Age, gender, tumour type and baseline biochemical parameters were similar between these patient groups. Figure 2 depicts the baseline electrolyte profiles in all recruited patients.

The age range of subjects analysed was 14 to 75 years, mean age 40.5 years (Figure 1). Case cancer type distribution was 40.5% breast cancer (BRCA), 16.2% non -Hodgkin's Lymphoma (NHL) and 15.3% chronic lymphocytic leukaemia (CLL). Most of the patients had advanced stage disease (stages III and IV). Only one patient with breast cancer had stage one disease. The percentage of patients with advanced stage disease was as follows; BRCA 78%, NHL 83, CLL 100 and HL 100 (Table 1).

Baseline electrolyte levels for 142 patients recruited in the study were within the normal laboratory reference range for individual electrolytes (Figure 2). The median value was used to summarise electrolyte changes as it is recognised as the best measure of central tendency when describing blood chemistry.

Documented percentage changes in electrolytes occurred as follows: Day one serum phosphates, potassium and uric acid showed a percentage rise of 73.5, 24.7 and 4.1% respectively; whereas serum calcium declined by 2.2%. The highest percentage increase occurred on day three when phosphates increased by 95.7% and potassium increased by 32.5%; changes in serum calcium and uric acid were negligible at –1.2% and + 4.1% respectively. Therefore on the basis of percentage change in electrolytes, only potassium and phosphate met the diagnostic criteria for TLS of increase by at least 25% from baseline (Figure 3).

Figure 1

Age distribution of the included and excluded subjects

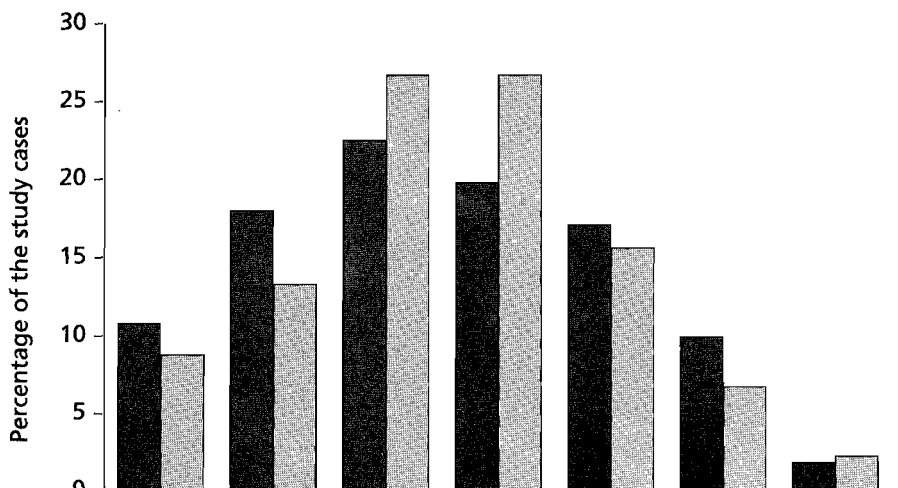


Figure 2

Baseline median serum electrolytes

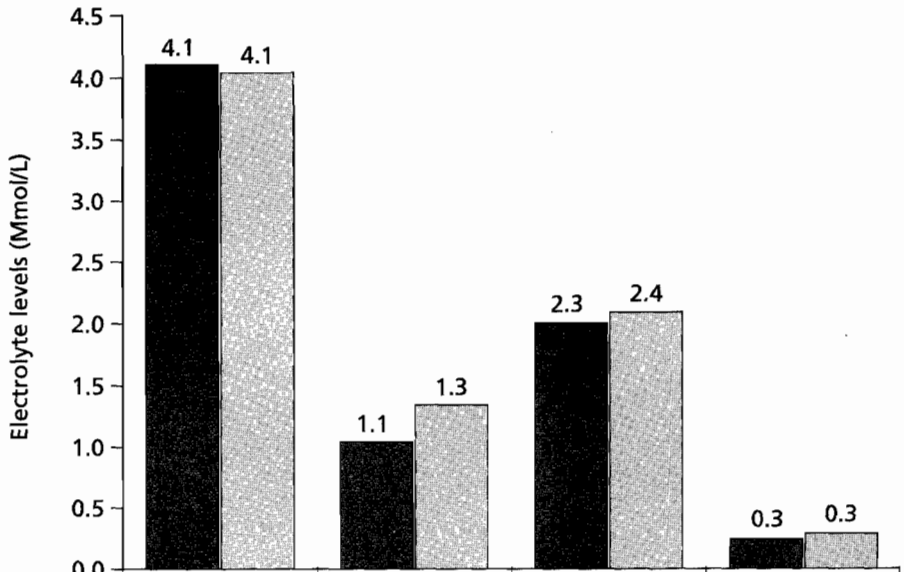


Table 1

Tumour types and stage of disease

Tumour	Number	Stage
Breast cancer (n = 45)	1	I
	9	II
	17	III
	18	IV
Non-Hodgkin's Lymphoma (n = 18)	3	II
	7	III
	8	IV
Chronic Lymphocytic Leukaemia	8	IV
Chronic Myeloid Leukaemia	9	IV
Hodgkin's Lymphoma (n = 6)	2	III
	4	IV
Others	4	IV
Not staged (AML,ALL,MM)	21	–
Total	111	–

Key: MM = Multiple myeloma; AML = Acute Myeloid Leukaemia; ALL = Acute Lymphocytic Leukaemia's.
Others included: Gestational trophoblastic disease , Rhabdomyosarcoma, Osteogenic sarcoma, Colon cancer, Ovarian cancer, Hepatoma, Fibrosarcoma, Metastases from unknown site and gastrointestinal stromal tumour.

Table 2

Potassium levels and hyperkalaemia development

Day	(%) K rise	Median K value mmol/l	Absolute hyperkalaemia mmol/l			
			n	≥ 6.0	≥ 6.5	≥ 7.0
0	73.5	4.0	0	–	–	–
1	88.3	5.1	19	4	3	3
2	95.7	5.4	21	10	–	3
3	94.2	5.2	–	–	–	–
4	–	–				

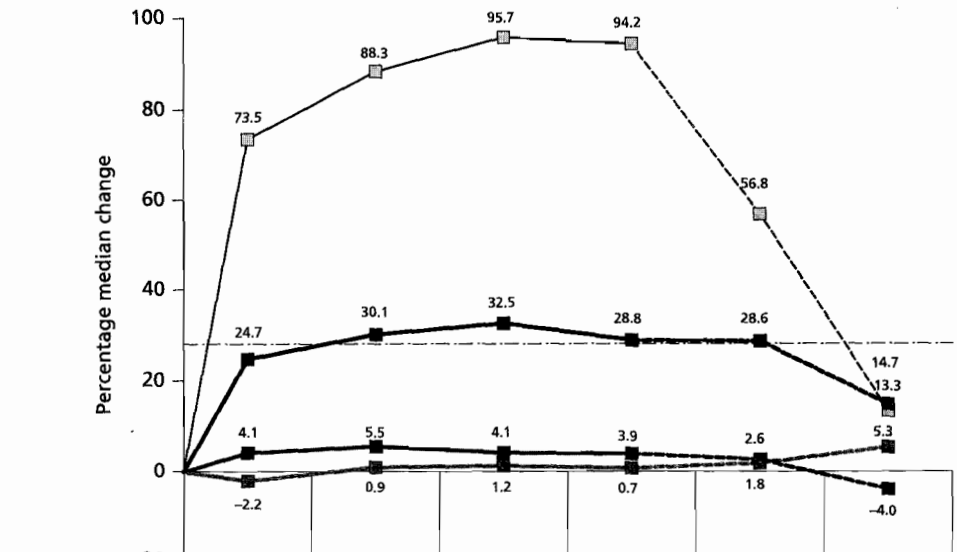
Table 3

Proportion of patients developing TLS by tumour type

Tumour	Total number	TLS positive	Incidence TLS % (95% C.I)
Breast cancer	45	0	0
Non-Hodgkin's lymphoma	18	14	77.8 (66.2 - 90.4)
Chronic myeloid leukaemia	9	7	77.8 (62 - 93.6)
Chronic lymphocytic leukaemia	8	8	100.0
Hodgkin's lymphoma	6	4	66.7 (45.5 - 87.9)
Multiple myeloma	5	2	40.0
Acute lymphoid leukaemia	4	3	75
Acute myeloid leukaemia	3	2	66.7
Choriocarcinoma	3	1	33.3
Osteogenic sarcoma	2	0	0
Ca colon	2	0	0
Rhabdomyosarcoma	1	1	100
Ca ovary	1	0	0
Hepatoma	1	0	0
Fibrosarcoma	1	0	0
Unknown metastases	1	0	0
Gastro-intestinal stromal tumour	1	0	0
Total	111	42	

Figure 3

Percentage changes in serum electrolytes



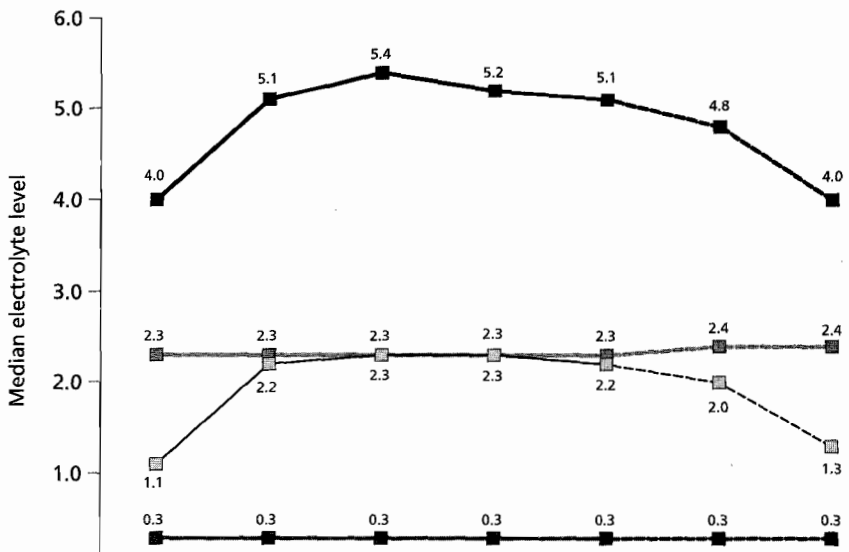
	Day 1	Day 2	Day 3	Day 4	Day 7	Day 15
Potassium	24.7	30.1	32.5	28.8	28.6	14.7
Phosphate	73.5	88.3	95.7	94.2	56.8	13.3
Calcium	–2.2	0.9	1.2	0.7	1.8	5.3
Uric acid	4.1	5.5	4.1	3.9	2.6	–4.0

Day of observation

NB: The dotted horizontal line indicates the 25% cut-off point. Only potassium and phosphates cross the line on day 1, 2, 7 and 15

Figure 4

Median changes in monitored biochemical parameters

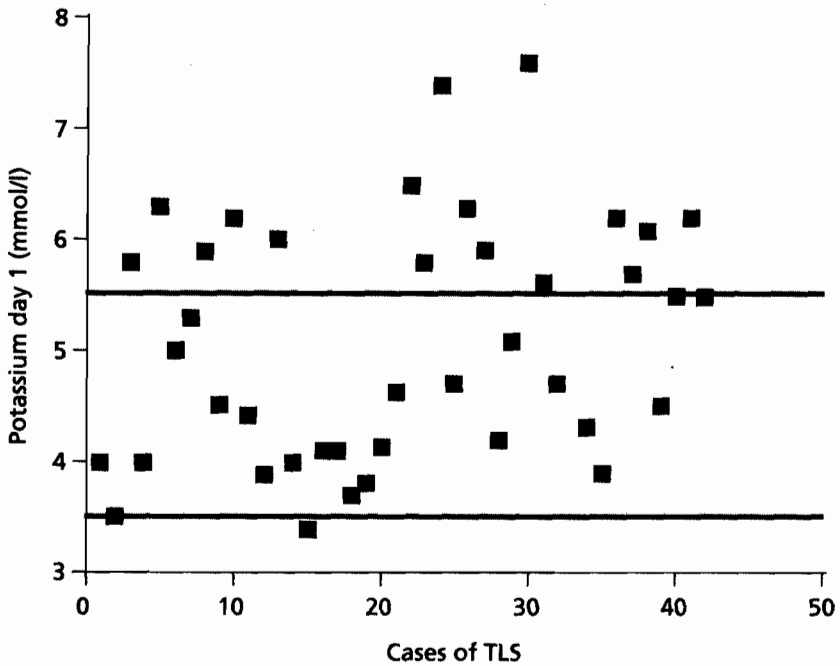


	Day 0	Day 1	Day 2	Day 3	Day 4	Day 7	Day 15
Potassium	4.0	5.1	5.4	5.2	5.1	4.8	4.0
Phosphate	1.1	2.2	2.3	2.3	2.2	2.0	1.3
Calcium	2.3	2.3	2.3	2.3	2.3	2.4	2.4
Uric acid	0.3	0.3	0.3	0.3	0.3	0.3	0.3

Day of observation

Figure 5

Distribution of serum potassium on Day one



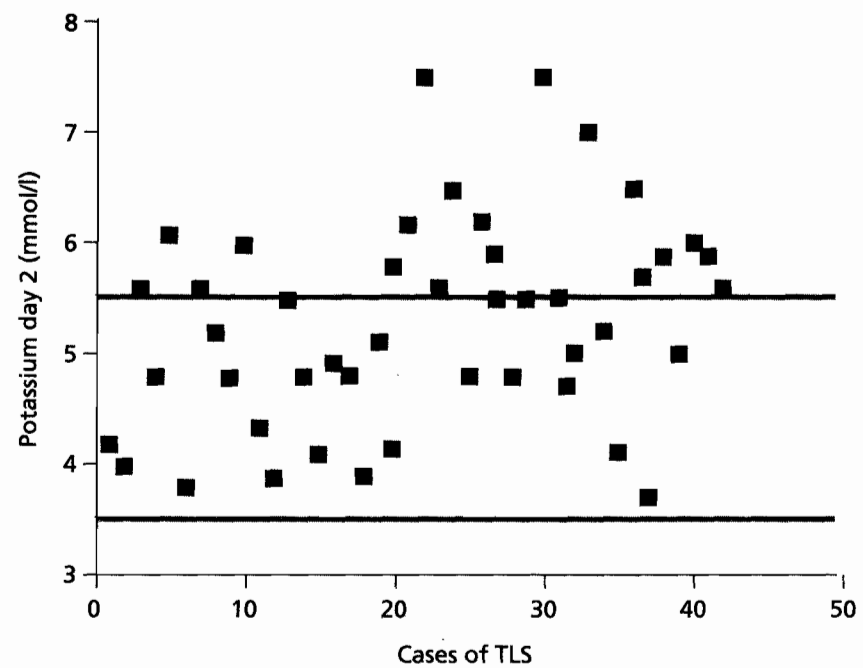
Key

Horizontal lines represent the normal laboratory reference range of 3.5 mmol/l to 5.5 mmol/l

Squares represent patients with TLS = 42

Figure 6

Distribution of serum potassium on Day two



Key

Horizontal lines represent the normal laboratory reference range of 3.5 mmol/l to 5.5 mmol/l

Squares represent patients with TLS = 42

Median changes in electrolytes are illustrated in Figure 4, and occurred as follows. Day one median serum phosphates increased from 1.1 mmol/l to 2.2 mmol/l whereas median serum potassium increased from 4.0 mmol/l to 5.1 mmol/l. The highest median values were seen on day two and three when phosphate was 2.3 mmol/l and potassium was 5.2 mmol/l. Median values for uric acid and calcium did not change significantly over time. The serum electrolytes showing significant change were potassium and phosphate, with both rising on day one after administration of chemotherapy and reached maximum levels on day two and three and commenced declining to baseline on day four.

Thus 42 patients showed more than a 25% rise defining biochemical parameters, representing a TLS incidence of 37.8% (C.I = 31.27 44.29), based on increase in serum potassium and phosphate, in a sample of 111 study subjects.

There was no change in serum calcium that met the criteria for laboratory TLS while only one patient was diagnosed with TLS based on increase in serum uric acid levels. Fifty percent of TLS cases occurred by day one and 95.2% by day three.

Only 2.4% of the cases occurred by day four and the cumulative percentage by day four was 97.6%.

Temporal resolution of TLS occurred at the following rates; 11.9 % by day two; 54.8% by day seven and 97.7% by the day 15. Only 2.4% of the cases had not resolved by day 15.

No cases of TLS were detected in patients receiving chemotherapy for breast cancer. The incidence of TLS on basis of cancer type is depicted in Table 2; with rates of 77.8% (95% C.I = 66.2 90.4) in 14 of 18 patients with NHL and 75% (95% C.I = 66.47–84.47) in 40 of 53 patients with haematological tumours. Only two of 58 (3.5%; 95% C.I = 1.55 – 8.45) patients with non-haematological tumours developed TLS. Eighteen of the patients with NHL had diffuse large cell lymphoma and all developed TLS.

Between day one and day two, 50% of the patients with TLS developed absolute hyperkalaemia and about half of these had potassium levels in excess of 6.0 mmol/l. On day one, 30% had severe hyperkalaemia (≥ 6.5 mmol/l) and this declined to 15% by day two. All cases of hyperkalaemia were managed conservatively with dextrose and insulin infusion. No patient was treated for hyperphosphataemia and none required renal replacement therapy. No treatment interruptions occurred on account of development of TLS in patients with NHL, as all cased had resolved by day 21. Two mortalities occurred on days five and six; a 21 year female with AML, FAB type M2 with serum potassium of 7.4 mmol/l and haemorrhagic thrombocytopaenia of 10×10^9 /l at time of demise; 24years female with abdominal rhabdomyosarcoma and uric acid at 0.45 mmol/l and potassium 5.9 mmol/l at the time of death. This translates to a TLS case fatality rate of 1.8%, however these deaths could not be directly attributable to TLS.

DISCUSSION

This report is the first from Kenya, and the region, to establish the frequency of chemotherapy-related TLS, and our findings of an incidence of 39%, utilising the case definition of Hande and Garrow is comparative to that of 42% reported by these authors (1). These authors however, only reported on non-Hodgkin's lymphomas; in our study when non-Hodgkin's lymphomas were analysed separately, the incidence of TLS was much higher at 70.8%. Utilising different case definitions, Cohen et al reported an incidence of 38.3% similar to that of 25% by Arseneau (10,11). Both studies, however were undertaken in the 1980's before the currently utilised definition, as proposed in 1983 by Hande *et al*. Arseneau used hyperkalaemia alone while Cohen used both hyperkalaemia and hyperuricaemia to define TLS.

With an average of 720 patients receiving chemotherapy annually at our institution, an average of 300, predominantly haematological patients, are annually at risk of developing TLS. Over 50% of these cases will occur on the first day and the majority (98%) by day four. This is particularly relevant to an outpatient chemotherapy strategy, which is our institutionally preferred policy, and suggests that closer follow-up is warranted over the first four days of initiating chemotherapy.

In our study, 95.2% of the TLS cases occurred in haematological malignancies and is consistent with other studies, which have shown that TLS is mainly a complication of chemotherapy for haematological malignancies (1). The factors predisposing haematological malignancies to the development of TLS include high chemosensitivity, high mitotic rate, large tumour bulk, and use of

intensive chemotherapy protocols. Published literature on TLS involving non-haematological malignancies is limited consisting only of case reports of clinically manifest TLS (12-16). In our study only two patients with non-haematological tumours developed TLS.

Only fifty per cent of patients developing TLS, between days one and three, had absolute hyperkalaemia compared to 86 and 96% with absolute hyperphosphataemia. This implies that using the laboratory reference levels for potassium alone to consider a diagnosis of TLS will miss about 50% of cases, while phosphate levels alone will miss only 4 -14%. Therefore serum phosphate was more sensitive for detection of TLS development compared to serum potassium. No morbidity related to development of hyperphosphataemia was discernable.

Between day one and day two, 50% of patients with TLS had absolute hyperkalaemia and about half of theses had potassium level in excess of 6.0 mmol/l. On day one, 30% of these had developed severe hyperkalaemia with potassium in excess of 6.5 mmol/l.; by day three the rate of severe hyperkalaemia had declined by half (Figures 5 and 6 and Table 2). One case fatality could be attributed to hyperkalaemia.

The absence of hyperuricaemia, in our study, is unusual because it is believed to be the most commonly observed derangement in patients with chemo-sensitive tumours (5,17-19,). One of the reasons for this finding may be the routine practice of prophylactic allopurinol in all the patients at risk.

No patient had a decline in serum calcium by 25% from baseline. This is because hypocalcaemia occurs secondary to hyperphosphataemia and since the phosphate elevation was moderate, it was not sufficient to cause hypocalcaemia.

The most common non-haematological tumour in this study was breast cancer (77.6%). None of the patients with breast cancer developed TLS. This is in contrast to the study by Gregory *et al.* (20) who studied 25 patients with breast cancer and reported a 25% incidence of TLS; however this study included patients with pretreatment renal dysfunction which is a known risk factor for development of TLS (21,22). The rarity of TLS in breast cancer has been ascribed to the low tumour mass at chemotherapy, as this is usually administered following mastectomy (23).

By end of the first week, about 45% of patients had not recovered from TLS. This is important in patients receiving weekly treatment schedules such as acute lymphocytic syndrome in which second course pretreatment derangement in renal function will predisposes patients to development of TLS.

In conclusion laboratory tumour lysis syndrome is common at KNH (38%) and mainly occurs in haematological malignancies. Most cases occur on the first day of chemotherapy, hyperkalaemia and hyperphosphataemia are the predominant biochemical defining manifestations.

ACKNOWLEDGEMENTS

To the doctors and nursing staff at KNH ward 8C and Haematology/ Oncology clinic for their co-operation; to DAAD/Moi University for funding part of the study and the Director, KNH for permission to publish these data.

RFFERENCES

1. Hande K.R. and Garrow G.C. Acute Tumour lysis syndrome in patients with high grade non-Hodgkin's Lymphoma. *Amer. J. Med.* 1993; **94:** 133-139.
2. Vogezang J.N., Nelimark A.R. and Nath A.K. Tumour lysis syndrome after induction chemotherapy of small-cell bronchogenic carcinoma. *J. Amer. Med. Assoc.* 1983; **249:** 513-514.
3. Van Oosterom A.T., Luc Y.D. and Ruswick R.V. Metabolic disturbances of tumours. Oxford text book of Oncology: Micheal P., Pinedo M.H. and Umberto V. Oxford Medical Publications. 1995; 2214-2215.
4. Hassancili H.S. and Jefrey T.R. Acute tumour lysis syndrome in a patient with mixed small cell and non-small cell tumour. *MAYO Clin. Proc.* 2002; **77:** 722-728.
5. Cairo M.S. and Bishop M. Tumour lysis syndrome: New therapeutic strategies and classification. *Brit. J. Haem.* 2004; **127:** 3-11.
6. Micheal B.D., Snehal T., John K.H., *et al.* Pathophysiology, clinical consequences and treatment of tumour lysis syndrome. *Amer. J. Med.* 2004; **116:** 546-554.
7. Tietz W.N., Pruden L.E. and Andersen S.O. Electrolytes and renal functions. In Tietz textbook of clinical chemistry, 2nd Eds. Burtis A.C. and Ashwood R.E. W.B. Saunders Company. 1994; 1354-1540. Cairo MS
8. Ronco P. Renal involvement in plasma cell dyscrasias, immunoglobulin-based amyloidoses and fibrillary glomerulopathies, lymphomas and leukemias. Oxford textbook of medicine, 4th edn. Warrel D.A., Cox

T.M., Firth J.K.D. and Benz E.J. Oxford University Press,Oxford. 2003; **3:** 406-407.

9. Copland B.E. Quality control in clinical chemistry. Theory, analysis and correlation. Ed. Kaplan L.A. and Pesce A.J. 2nd Edn. CV Mosby Company. 1989; 270-289.
10. Cohen L.F., Balow J.E., Magrath I.T., *et al.* Tumour lysis syndrome: A review of 37 patients with Burkitts lymphoma. *Amer. J. Med.* 1980; **68:** 486-491.
11. Arseneau J.C., Bagley C.X.M., Anderson T. and Canellos G.P. Hyperkalemia: A sequel to chemotherapy of Burkitt's lymphoma. *Lancet.* 1973; **1:** 10-14.
12. Sklarin N.T. and Marakham M. Spontaneous recurrent tumour lysis syndrome in breast cancer. *Amer. J. Clin. Oncol.* 1995; **1807:** 71-73.
13. Stark M.F., Dyer M.C. and Coonley C.J. Fatal acute tumour lysis syndrome with metastatic breast carcinoma. *Cancer.* 1987; **60:** 762-764.
14. Drakos P., Bar-Ziv J. and Catano R. Tumour lysis syndrome in non-haematological malignancies. Report of a case and review of the literature. *Amer. J. Clin. Oncol.* 1994; **17:** 502-505.
15. Bilgrami S.F. and Fallon B.G. Tumour lysis syndrome after combination chemotherapy for ovarian cancer. *Med. Pediatr.* 1993, **21:** 521-524.
16. Blanke C.D., Hemmer M.P. and Witte R.S. Acute tumour lysis syndrome with choriocarcinoma. *South Med. J.* 2000; **93:** 916-919.
17. De conti R.C. and Calabresi P. Use of allopurinol for prevention and control of hyperuricemia in patients with neoplastic disease. *N. Engl. J. Med.* 1966; **274:** 481-486.
18. Dann E.J., Gills Aaron P., Okon E., *et al.* Xanthine nephropathy in a patient with lymphosarcoma treated with allopurinol. *N. Engl. J. Med.* 1970; **283:** 354-357.
19. Coiffier B., Mounier N., Bologna S., *et al.* Efficacy and safety of rasburicase (recombinant urate oxidase) for the prevention and treatment of hyperuricaemia during induction chemotherapy of aggressive non-Hodgkin's lymphoma. *J. Clin. Oncol.* 2003; **21:** 4402-4406.
20. Gregory P.K., Bassel D. and Mann L.V. Tumour lysis syndrome in small cell carcinoma and other solid tumours. *Amer. J. Med.* 1997; **103:** 363-367.
21. Boccia R.V., Longo D.L., Lieler M.L., *et al.* Multiple recurrences of tumour lysis syndrome in an indolent non-Hodgkin's lymphoma. *Cancer.* 1985; **56:** 2295-2297.
22. Fassa B.T.A., Desikan K.R., Siegel D., *et al.* Tumour lysis treatment complicating high dose treatment in patients with multiple mycloma. *Brit. Med. J.* 1999; **105:** 938-941.
23. Powler J.J. and Smith I.E. The breast Bailey and Love's short practice of surgery. 23rd Edition. Russell R.C.G., Norman W., Balstrode C.J.K. Publisher. Arnold. 2000; 749-772.