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Tumor lysis syndrome: a critical review

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Abstract

In recent era cancer has become either a major cause of death in most of the parts of world or can leads to metabolic disorder named as Tumor lysis syndrome (TLS). TLS occurs as a massive lysis of malignant cells and the abrupt release of intracellular contents into the systemic circulation. It can prompt electrolyte imbalances in the body which causes hyperuricemia, hyperkalemia, hyperphosphatemia and hypocalcemia. It is the eventual outcome of anticancer treatment yet it can grow at the same time as well (spontaneous TLS). This review centers around the pathophysiology, metabolic variations from the normal, arrangement, the study of disease transmission, etiology, aversion, populace in danger, prescribed eating regimen and part of palliative care in this metabolic issue.

Keywords*: Cancer; Tumor lysis syndrome; electrolyte imbalance; diet; palliative care*

Introduction

Cancer holds the maximum mortality rates in most of the developing or developed countries. Tumor lysis syndrome (TLS) is a group of metabolic irregularities that can happen as an entanglement amid the treatment of cancer, where a lot of tumor cells are killed off (lysed). In the meantime, the end products are discharged into the circulatory system through narrow blood vessels (Howard *et al*., 2011). These discharged products are usually potassium (K^+), phosphate $(PO_4)^{2-}$, nucleic acid, lactate dehydrogenase etc. which enters the blood in human body. This happens most usually after the treatment of lymphomas and leukemia's (Gilbert

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and Wright, 2015). In oncology and hematology, this is a conceivably lethal complication, and patients at expanded hazard for TLS ought to be closely observed some time before, amid, and after their course of chemotherapy (Edeani and Shirali, 2016). TLS can be broadly divided into 3 main categories i.e. No syndrome, clinical TLS and laboratory TLS. In no syndrome, cell lysis occurs with only negligible changes in the human body chemistry. On the other hand, in laboratory TLS the lab values are quite unusual but they have not yet initiated clinical manifestations whereas in clinical TLS body disturbance reach a level that has major clinical consequence and requires urgent intervention (Howard *et al*., 2011). This is usually a subcategory of laboratory TLS, it can only be declared if at least one clinical criteria is present and the levels are either below or above normal levels, whereas laboratory TLS is defined when biochemical markers vary within 3-7 days span of chemotherapy (3 days before the therapy begins and 7 days after the therapy is done) (Cairo and Bishop, 2004). **Table 1** clearly states the various categorizations given by Cairo and Bishop in (2004) as per laboratory and clinical trials. Being major diagnostic criteria, TLS had been categorized into Grade I to Grade V. Certain variables such as creatnine levels, cardiac arrhythmia and seizures are present but in all these variables Grade V had been identified as the most critical stage in which the person is not able to survive. **Table 2** depicts the Cario-Bishop grading system of TLS which is medically accepted across the globe. This grading system is applicable only in the case of adults.

Metabolic abnormalities

Hyperkalemia

Hyperkalemia is a potentially threatening electrolyte disorder appreciated with greater frequency in patients with renal disease, central system failure (Palmer, 2004). Clinical manifestations include nausea, anorexia, vomiting and diarrhea. As the complication level

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increases, neuromuscular and cardiac abnormalities (peaked T-waves on electrocardiogram; systole ventricular tachycardia or fibrillation) also increase (Montford and Linas, 2017). The traditional view states that hyperkalemia can be reliably diagnosed by electrocardiogram (ECG) (Ingelfinger, 2015). The kidneys play a major role in maintaining potassium homeostasis by matching potassium intake with potassium removal. Urinary excretion of potassium commences in the distal convoluted tubule and is further regulated by the eloign nephron and collecting duct. Therefore, reduction and damage of nephron function as a consequence of kidney disease results in renal preservation of potassium. The main government bodies of this process are aldosterone and serum potassium level. It indicates the clear inability of kidneys to excrete the massive quantities of potassium released by lysed tumor cells.

Hyperphosphatemia and Hypocalcaemia

Hyperphosphatemia (≥2.1 mmol/L in children and ≥1.45 mmol/L in adults) develops from 24-48 hours after the process of chemotherapy begins (Jeha, 2001). With the increase in the release of phosphate $(PO_4)^{2-}$at intracellular levels, renal threshold value for phosphate excretion is crossed leading to hyperphosphatemia (Kalemkerian *et al*., 1997). Normal mature lymphoid cells release 4 times more intracellular phosphate as compared to malignant hematological cells (Flombaum, 2000). Moreover, at the times of acute destruction of tumor cells during chemotherapy inhibits hasty reuse of phosphate for newly synthesized tumor cells (Jones *et al*., 2015). Severe hyperphosphatemia may result in hypocalcaemia, metastatic calcification, intrarenal calcification, nephrocalcinosis, nephrolithiasis and obstructive uropathy. Muscular, cardiovascular and neurological complications such as muscle cramps, cardiac arrhythmia and seizures are the common after effects when the levels increase at an alarming rate (Cairo and Bishop, 2004; Jeha 2001; Sewani and Rabatin, 2002).

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Hyperuricemia

After the initiation of cancer treatment, within 48 to 72 hours hyperuricemia develops (Wilson and Berns, 2012). When the tumor lysed cells undergo purine metabolism, they are metabolized into uric acid. The array of serum uric acid exceeds above 8 mg/dL and 25% from the standard, the pathophysiology of intense acute renal failure in TLS becomes multifactorial i.e., either by uric acid nephropathy or by volume consumption (Cairo and Bishop, 2004).

Epidemiology

The frequency of TLS fluctuates widely, ranging from spontaneous reports in certain strong malignancies to 26.4% rate portrayed in high review beta cell lymphoblastic leukemia. The most critical hazard for TLS is found in tremendous volume in exceedingly metabolic malignancies, for instance, lymphoblastic leukemia, Burkitt lymphoma, lymphoblastic leukemia while solid tumors and steadily developing tumors bring down the dangers of TLS (Singh *et al*., 2017). Unconstrained TLS are generally seen in high grade hematological malignancies (Kalemkerian *et al*., 1997). Unconfined TLS are commonly witnessed in high review hematological malignancies (Singh *et al*., 2017).

Etiology

TLS can be caused by various factors such as

Chemotherapy

Chemotherapy is the use of anti-cancer medicines to destroy cancer cells.it is commonly known as “chemo”. The type of drug that is used will depend on the type of disease the patient has and what part of the body it started in. Chemotherapy might be given with a therapeutic plan (which quite often includes mixes of medications), or it might mean to draw out life or to decrease symtoms (palliative chemotherapy). Chemotherapy is one of the real

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classifications of the therapeutic train particularly committed to pharmacotherapy for restricting the growth of tumor cells, which is known as medicinal oncology (Wood *et al*., 2005).

By basic utilization, the term chemotherapy has come to enhance rather non-particular intracellular toxic substances, particularly identified with repressing the procedure of cell division known as mitosis, and by and large prohibits operators that all the more specifically piece extracellular development signals (i.e. blockers of flag transduction). To stay away from these undertones, as of late created treatments (against particular atomic or hereditary targets) which restrain development advancing signs originating from great endocrine hormones (basically estrogens for bosom tumor and androgens for prostate disease) are called hormonal treatments, while the restraint of other development advancing impacts (particularly those related with receptor kinases is known as focused treatment (Lewis *et al*., 2011). According to Niederhuber *et al*., (2013), most therapy sessions are given through a drip straight into the bloodstream i.e. intravenously (IV) whereas others are given in the form of tablets or capsules. If the patient is being treated for skin cancer then a topical chemotherapy cream may be used (Niederhuber *et al.*, 2013).

Antibody therapy

It is a type of immunotherapy that utilizations monoclonal antibodies (mA). The goal is that this treatment will empower the patient's invulnerable framework to assault those cells. All the more, antibodies have been utilized to tie to particles associated with T-cell control to evacuate inhibitory pathways those square T-cell reactions (Scott *et al*., 2012). This is known as immune checkpoint treatment. Hostile to growth monoclonal antibodies can be focused against dangerous cells by a few instruments (Waldman, 2003). Ramucirumab is a recombinant human monoclonal immune response and is utilized as a part of the treatment of

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cutting-edge malignancies, for example, leukemia, lymphoma, melanoma and so forth (Adams and Weiner, 2005). It is conceivable to make monoclonal antibodies that are particular to any outside cell surface target. Innovative work is in progress to make antibodies for sicknesses, for example, rheumatoid joint inflammation, alzheimer's malady, different sclerosis, Ebola and different sort of cancers (Scott *et al*., 2012).

Corticosteroid therapy

Cortecosteroids are commonly used for the treatment of patients suffering from advance cancer, i.e. Stage III, IV and V. Most commonly used corticosteroids in European countries are prednisone, prednisolone, methylprednisolone, dexamethasone, and hydrocortisone (Wooldridge et al., 2001). The use of corticosteroids in advanced cancer revolves around their glucocorticoid effects, combined with an avoidance of the salt-retaining properties that characterize mineralocorticoids. Corticosteroids mimic the effects of hormones your body produces naturally in your adrenal glands, which sit on top of your kidneys. When prescribed in doses that exceed your body's usual levels, corticosteroids suppress inflammation. This can reduce the signs and symptoms of inflammatory conditions, such as arthritis and asthma.

Corticosteroids also suppress your immune system, which can help control conditions in which your immune system mistakenly attacks its own tissues (Wooldridge et al., 2001). This therapy induces cell death and allows rapid release of intracellular substances which leads to metabolic irregularities. Patients treated with corticosteroid undergo some degree of renal suppression thus, blunting or preventing normal renal response (Cancer research UK). To avoid this situation, Oncologists prefer giving intermittent doses of steroids so as to prevent hypersensitive reactions. Other risks associated with the usage of these steroids are insomnia, peptic ulcer disease, dyspepsia, anxiety, etc. One can inhale corticosteroids by mouth, inhaler or internasal spray, by injection or by creams and ointments which contains corticosteroids.

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Radiotherapy

Radiation refers to the waves of energy such as light or heat whereas radiotherapy deals with the treatment of oncological disease through ionizing radiations such as X-rays. The subspecialty of oncology concerned with radiotherapy is called radiation oncology. Radiation treatment is usually connected to the dangerous tumor in view of its capacity to control cell development. Ionizing radiation works by harming the DNA (Deoxyribonucleic corrosive) of dangerous tissue prompting cell demise. To save typical tissues, (for example, skin or organs which radiation must go through to treat the tumor), molded radiation shafts are pointed from a few edges of presentation to converge at the tumor, giving a considerably bigger consumed dosage there than in the encompassing, sound tissue (Wilson and Berns, 2012). Other than the tumor itself, the radiation fields may likewise incorporate the depleting lymph hubs on the off chance that they are clinically or radio intelligently required with tumor, or if there is believed to be a danger of subclinical dangerous spread. It is important to incorporate an edge of typical tissue around the tumor to take into account vulnerabilities in day by day set-up and inside tumor movement. These vulnerabilities can be caused by inward development (for instance, breath and bladder filling) and development of outside skin marks in respect to the tumor position. As per reports, there are 2 sorts of radiotherapy used upon patients. First being, external beam radiotherapy which is more ordinarily utilized treatment finished with the assistance of Linac (straight quickening agent) on which the patient is put. Light emission is engaged by an outer machine onto the treatment territory of the patient's body. This is otherwise called 3-D conformal radiotherapy. As per the size of the tumor, intensity of radiations is confined. But the drawback of this is that it affects the adjacent healthy cells thus leading to reduction in the number of healthy cells. Other therapy which is commonly used is sealed source radiotherapy. In this, the radioactive material is placed in direct contact with the

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tumor inside the human body. Radioactive material can be placed in the form of capsule, wire or sphere depending upon the size and area affected by the tumor.

AKI

It stands for acute kidney infections or diseases. AKI in TLS may be either due to the aforementioned effects of acute urate nephropathy or hyperphosphatemic nephropathy or hyperphosphatemic nephro calcinosiumora combination of the two (Abu- Alfa and Yunus, 2010). Some studies have suggested that uric acid to creatnine ratio of 1, may be specific to uric acid nephropathy but another study has noted high uric acid to creatnine ratios in AKI from other etiologies. The association between AKI and TLS has been demonstrated across various populations and tumor subtypes. Annemans *et al*., (2003) found that 45% patients suffer from AKI if already being patients with leukemia and NHL also having TLS. A smaller pediatric cohort of B-cell NHL or Acute Lymphocytic Leukemia (ALL) noted renal insufficiency in 20% percent of the study. Thus, children are probably at low risk as compared to adults. **Figure 1** depicts the hypothetical mechanism of event that might take place one after the other and lead to severe complications.

Preventive measures

It is fundamental to recall that the aversion of sickness has been constantly more financially efficient than the treatment of a set up illness (Mirrakhimov, 2015). Patients' administration ought to be centered around the premise of the kind of disease and certain biochemical parameters associated to it (Coiffier *et al*., 2008). A few highlights are the pillar of treatment for the counteractive action of TLS in patients experiencing dynamic treatment. To begin with, all patients at middle of the road and high hazard ought to be effectively hydrated with IV fluids.

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Second, people at middle of the road danger of TLS ought to be begun on ***allopurinol*** no less than 24 to 48 h before chemotherapy or radiation treatment to diminish the danger of uric corrosive nephropathy (Hochberg and Cairo, 2008). Patients who don't endure oral pharmaceutical, for example, those with serious queasiness, regurgitating, or adjusted capacity of the gastrointestinal tract can be given allopurinol IV. The prescribed dosage of allopurinol is up to 800 mg daily orally or 100 mg for every square meter, and up to 600 mg daily for IV plan. In spite of being a sheltered specialist, rasburicase ought not to be utilized as a part of pregnant or lactating patients because of constrained information on wellbeing (pregnancy class C medication) and discharge into bosom drain (Lopez *et al*., 2013). Uric corrosive levels fundamentally diminished by 85% with rasburicase contrasted and 12% with allopurinol inside 4 hours of medication organization (Syrimi *et al*., 2017). Febuxostat does not require measurements alteration in patients experiencing renal ailments (Mirrakhimov *et al*., 2015). But, absence of confirmations makes it wrong for use. Another way of turning things in TLS is urine alkalization as alkaline pH promotes the solubility of uric acid and its removal (Edeani and Sherali, 2016).

Why Dialysis?

For pediatric and grown-up patients at high danger of TLS, cytotoxic chemotherapy should just be controlled once patients are situated in an office with prepared access to dialysis. Despite the fact that dialysis utilization has been decreased since the presentation of rasburicase, hike of 3% of patients (1.5% of pediatric patients and 5% of grown-up patients) still need to experience dialysis keeping in mind the end goal to expel poisons from the body. In context to high risk patients, a nephrologist should therefore be notified in advance. Oncologist and Nephrologist needs to have good co-ordination in order to slow down the

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process. Once the urine level is low, healthcare specialist needs to put in attention towards the raised phosphate levels and decreased calcium levels.

Population at risk

The major factor which increases the proximity of TLS is old age as the filtration rate (glomerular filtration rate) is decreased. Advancing age predisposes to TLS and renal reserve would complicate the situation at times (Howard *et al*., 2011). Patient undergoing therapy has poor or decreased oral intake due to lack of appetite or nausea. These medications are observed due to increased medication and lack of sleep. On the other hand, cancer patients suffer also from diarrhea, vomiting due to increased medication and lack of sleep. With decreased volume status, utilization of inhibitors of angiotensin changing over compound and angiotensin columnist blockers is favored (Mirrakhimov *et al*., 2015). Consider that benchmark kidney disorder is an entrenched hazard factor for TLS.

Other significant hazard factor is a kind of harm and the stage. Cairo and Bishop, (2004) stratified disease into 3 risk groups: a high hazard, intermediate risk group, and a generally safe i.e. low risk group. Transitional hazard malignancies incorporate AML with a WBC in the vicinity of 25000 and 100000, ALL with WBC < 100000 and a LDH of not as much as twice ULN, beginning time Burkitt lymphoma with a LDH of not as much as twice ULN, and diffuse substantial B-cell lymphoma with a benchmark increment in LDH of twice ULN yet non-bulky sickness. Generally safe infections incorporate sluggish lymphomas, endless lymphocytic leukemia, and constant myeloid leukemia in the perpetual stage, AML with WBC check < 25000 and a LDH hoisted to not as much as twice ULN, various myeloma, and strong diseases (Cairo and Bishop, 2004). In this way, amid our hazard stratification we gave careful consideration to patients with Burkitt's lymphoma/leukemia, ALL, AML, and diffuse extensive B cell lymphoma.

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Recommended diet

Patients suffering from TLS are recommended "Neutropenic Diet". According to Wilson and Berns, (2002) basic mantra of neutropenic diet is a low fiber diet. Whole of fresh fruits and vegetables are avoided including all fresh garnishes. Uncooked meats, seafood and eggs are also non advisable to the patients suffering from TLS. Meat should be cooked to the "well-done" stage and eggs should be thoroughly cooked (no runny yolk). Opting for vacuum packed lunch meats rather than freshly sliced meats are recommended. Cooked vegetables, canned fruits and fruit juices are fit for consumption. In neutropenic diet, it is advisable not to consume salad bars, fruit bars, deli counters, raw nuts, yogurt and its products with live and active cultures. Consumption of pasteurized dairy products is advisable. And it is advisable to be safe in the way one handle foods and wash hands before handling food. Keep hot food hot and cold food cold (Sonbol *et al*., 2015).

Palliative care

WHO characterizes palliative care as "an approach that enhances the personal satisfaction of patients and their families by methods for early distinguishing proof, faultless evaluation, treatment of agony and different issues, physical, psychosocial and spiritual." Palliative care group incorporates an oncologist and oncology nurture which is for the most part in view of chemotherapy or radiation plan. Standard subsequent meet-ups are arranged. Legitimate access to 24 hours available to come back to work benefit (oncologist or clinical partner) and healing facility administrations are given (Zimmermann *et al*., 2014).

As suggested by Rajgopal (2015), home to one-sixth of the world's population, India has a huge burden of suffering from life-limiting diseases. Less than 1% of its population has access to pain relief and palliative care. There has been a lot of progress in palliative care in India, but the fact remains that despite the passing of almost a quarter of a century of

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palliative care activity in the country, even today palliative care reaches only about 1% of the people in India. Thus, the recent declaration by the World Health Assembly asking all member states to integrate palliative care with routine health care comes as a major tool in advocacy and hopefully will boost the current efforts.

Future Prospective and Conclusion:

TLS is a potentially devastating after effect amid the treatment of various malignancies. Proper preventive measures should be taken and if the scenario worsens then the treatment should begin without any delay. Dietary guidelines should be followed properly. Though lack of evidences still makes it hard to accept neutropenic diet globally but still literature has shown its positive effects in patients with high burden risk. Future research elucidating the various untouched aspects of TLS, recommended diet can be worked upon in depth.

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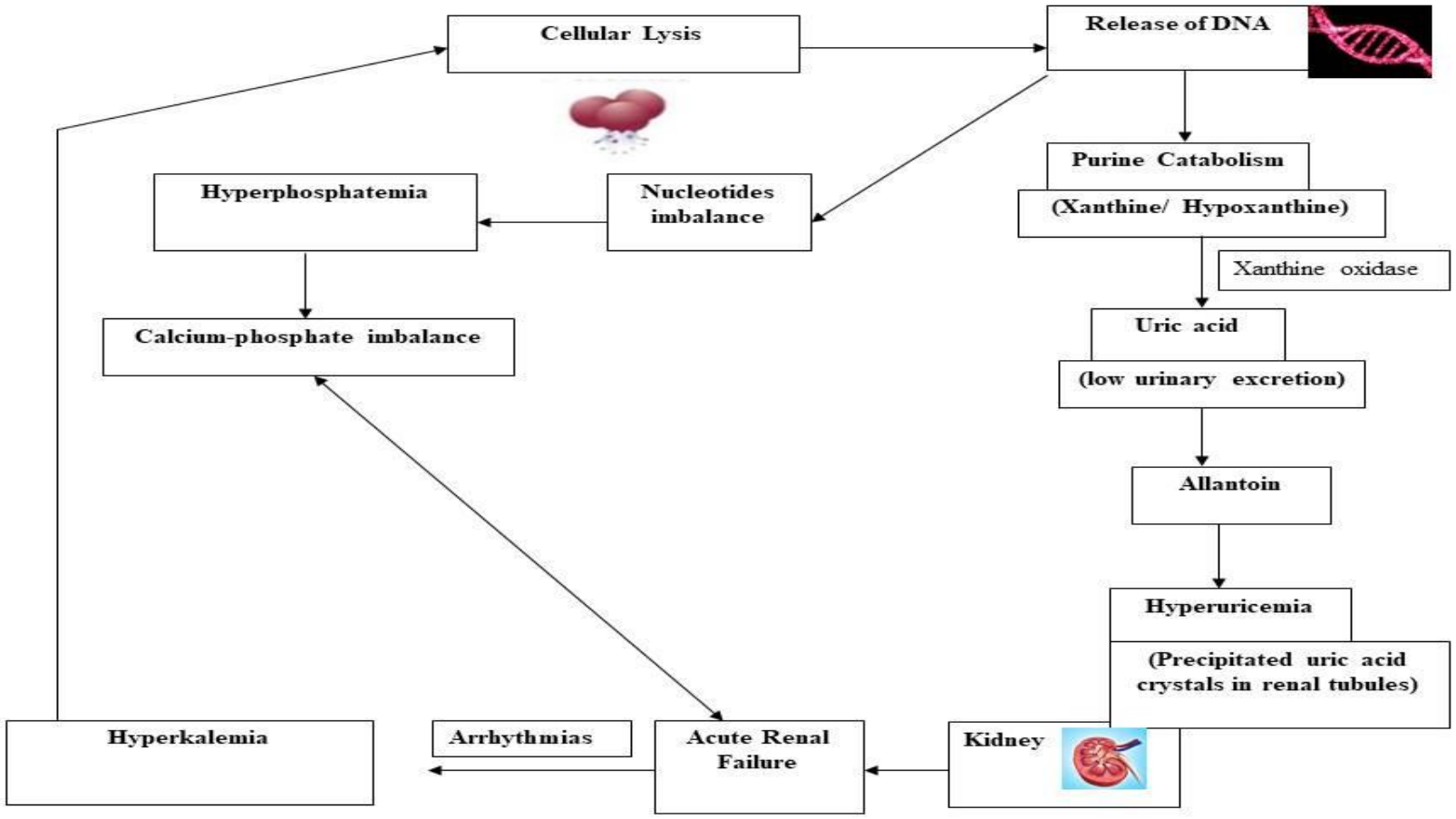

Figure 1: Pictorial representation of series of events leading to Tumor lysis Syndrome (TLS)

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Table 1: Cairo- Bishop classification of TLS on the basis of laboratory and clinical trials

Laboratory TLS	Clinical TLS	Variance levels
Uric acid > 8.0 mg/dl		25% hike
	Creatnine >1.5* the upper limit	
Potassium >6.0 mg/dl	Acute Kidney illness	25% hike
Phosphorus > 4.6 mg/dl	Cardiac arrhythmia	25% hike
Calcium <7.0 mg/dl	Seizure, Tetany etc.	25% decline

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Table 2: Grading system of TLS for adults

Variable	Grade0	Grade I	Grade II	Grade III	Grade IV	Grade V
Creatnine	None	1.5 times	>1.5-3.0 times ULN.	>3.0-6.0 times	>6 times ULN	Death

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		ULN		ULN.		
Cardiac arrhythmia	None	Intervention not indicated	Not attributed to chemotherapeutic agent.	Incompletelly controlled or controlled with the help of device	Life threatening i.e. arrhythmia, hypotension, syncope, shock). Cardiac arrhythmias not attributed to chemotherapeutic drugs	Death
Seizures	None	Nil	Generalised seizure; well controlled by anticonvulsants; infrequent seizures which donot interfere with daily life activities.	Conciousness is altered; poorly controlled seizure disorder	Prolonged, repitative and difficult to control seizures	Death

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Abbreviation: ULN- upper limit of normal (In case of creatnine contents, rise in creatnine levels are not attributed to chemotherapeutic agents)

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Table 3: Electrolytes and their complications

Electrolyte	Reference Range	Pathophysiology	Clinical consequence	Treatment
Potassium	3.5-5.0 mmol/L	Rapid expulsion of intracellular K^+ into the circulation due to cell lysis.	Adverse skeletal (weakness, tissue breakage) and cardiac (Ventricular, arrhythmia) manifestations	Glucose, Sodium bicarbonate, K^+ binding resins, dialysis
Phosphate	3-5 mg/dL	Release of intracellular PO4- either due to cell lysis or due to renal function	Muscle cramps, arrthymias, tetany, seizures	Dialysis, phosphate binders

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			Renal failure (nephropathy)	
Uric acid	8 mg/dL	Cell lysis leads to increased levels of purine nucleic acids that convert to uric acid after metabolism		Dialysis, hydration, alkalization of xanthine oxidase inhibitors
Calcium	8.6-10.2 mg/dL	Precipitation of calcium phosphate complex due to rapid increase in the concentration of phosphate.	Muscle cramps, seizures, renal failure, tetany, arrhythmias	Calcium gluconate

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(Adapted from: Cairo and Bishop, 2004) Abbreviations: mmol- milimoles mg- miligrams; dL- deciliters, K^+- potassium