# MINI-REVIEW

# Tumour Lysis Syndrome: Implications for Cancer Therapy

## Denish Mika, Sabrina Ahmad, C Guruvayoorappan*

## Abstract

   The tumour lysis syndrome (TLS) is a group of metabolic abnormalities caused by rapid and unexpected release of cellular components into the circulation as a result of massive destruction of rapidly proliferating malignant cells. It usually develops in patients with hematologic malignancies like acute lymphoid leukemia, non-Hodgkin and Burkitt's lymphoma after initiation of chemotherapy or may, rarely, occur spontaneously. Though TLS is seldom observed in relation to solid tumours, there have been reports of connections with examples such as lung, liver, breast, gastric carcinomas. The clinical manifestations of TLS include hyperuricemia, hyperkalemia, hyperphosphatemia and hypocalcemia. These indications if untreated lead to life-threatening complications such as acute renal failure, cardiac arrhythmias, seizures, and eventually death due to multiorgan failure. Therefore early detection of TLS is of vital importance. This can be accomplished by identification of high risk patients, implementation of suitable prophylactic measures andmonitoring of the electrolyte levels in patients undergoing chemotherapy.

**Keywords:** Tumour lysis syndrome - clinical manifestations - management - hyperkalemia

## Introduction

Tumour lysis syndrome (TLS) is the development of an array of metabolic disturbances that may occur either spontaneously or in response to cancer therapies. It results when a huge number of rapidly dividing cancer cells, particularly leukemia and lymphoma, are killed or lysed by cytotoxic therapy such as chemotherapy and radiation. Normal intracellular components of cells include potassium, phosphorus and nucleic acids. These intracellular ions are present in large amounts in cancer cells as compared to those in normal cells.

When malignant cells are killed by therapy they release their contents into the systemic circulation, which accumulate faster in the body than being eliminated from the body and the body's homeostatic mechanisms find it difficult to cope with. The release of these intracellular contents cause metabolic disturbances, which in turn manifest into life threatening complications such as hyperkalemia, hyperphosphotemia, hypocalcemia and hyperuricemia. Tumour lysis also releases cytokines that cause a systemic inflammatory response syndrome and often multiorgan failure (Hijiya et al., 2005; Nakamura et al., 2009; Soares et al., 2009).

During the early stages, some patients do not experience any symptoms of TLS but have abnormal laboratory values, which is suggestive of its succession. Laboratory results will show high potassium, uric acid and phosphorus levels and low calcium levels in the blood. Patients with TLS may suffer from initial symptoms of TLS comprising of nausea, shortness of breath, irregular heartbeat, clouding of urine, joint discomfort, etc. If untreated it may progress to critical conditions such as acute kidney failure, cardiac arrhythmias, and seizures. However, TLS is treatable if properly managed.

## Classification of TLS

At present there is no universal accepted system for classification of TLS. Hande and Garrow proposed the most comprehensive classification system for TLS. They classified TLS into Laboratory TLS (LTLS) and Clinical TLS (CTLS) (Hande and Garrow, 1993). This system makes a distinction between patients who do not require therapeutic medication versus those who experience life-threatening abnormalities. Cairo and Bishop developed a modified version of the Hande-Garrow classification system in an attempt to address the limitations of this classification system (Cairo and Bishop, 2004). According to this classification, LTLS is considered to be present if two or more serum values of uric acid, potassium, phosphate or calcium are above or below normal and if they change by 25% within 3 days before the start of the therapy or 7 days after the commencement of the treatment. The relevant classification is presented in Table 1.

CTLS requires LTLS to be present along with'one or more clinical complications such as renal insufficiency, cardiac arrhythmias, and seizures as described in Table 2. The grade of CTLS is defined by the maximal grade of clinical manifestation as detailed in Table 3 (Cairo and Bishop, 2004; Del Toro et al., 2005).

*Department of Biotechnology, Karunya University, Coimbatore, India *For correspondence: gurukarunya@gmail.com*

## Table 1. Cairo-Bishop Definition of Laboratory Tumour Lysis Syndrome.

Criteria for classification of laboratory tumour lysis syndrome (Cairo and Bishop, 2004)

| | |
|---|---|
| Uric acid | ≥8 mg/dL or 25% increase from baseline |
| Potassium | ≥6 mEq/L or 25% increase from baseline |
| Phosphate | ≥4.5 mg/dL in adults, >6.5 mg/dL in children or 25% increase from baseline |
| Calcium | ≤7 mg/dL or 25% decrease from baseline |

## Table 2. Cairo-Bishop Definition of Clinical Tumour Lysis Syndrome

Criteria for classification of clinical tumour lysis syndrome

1. Cardaic dysrhythmia, sudden death
2. Seizures
3. Increase in creatinine level of 0.3 mg/dL or presence of oliguria[a]

[a]Oliguria is defined as an average urine output of <0.5 ml/kg/h for 6 h, (Cairo and Bishop, 2004).

## Table 3. Grading System for Tumour Lysis Syndrome

| Grading system for tumour lysis syndrome | | | | | | |
|---|---|---|---|---|---|---|
| | Grade 0 | Grade I | Grade II | Grade III | Grade IV | Grade V |
| LTLS | - | + | + | + | + | + |
| Creatinine[a] | ≤1.5 ULN | 1.5 ULN or creatinine clearance 30-45 mL/min | 1.5-3 UNL or creatinine clearance 10-30 mL/min | 3-6 UNL or creatinine clearance 10-20 mL/min | >6 ULN or creatinine clearance <10 ml/min | Death[b] |
| Cardiac arrhythmia | None | Intervention not indicated | Non-urgent intervention indicated | Symptomatic and incompletely controlled or controlled with device | Life threatening (arrhythmia associated with chronic heart failure, shock) | Death[b] |
| Seizure | None | - | One brief generalized seizure; seizures well-controlled by anti-convulsants or sporadic focal motor seizures not interfering with activities of daily living | Seizures in which consciousness is altered; poorly controlled seizure disorder, with break-through generalized seizures despite medical intervention | Seizures of any kind which are long-lasting, recurring or difficult to control (e.g. status epilepticus) | Death[b] |

LTLS=laboratory tumour lysis syndrome; ULN=upper limit of normal. [a]Creatinine serum creatinine is 1.5 times greater than the institutional ULN below age/gender defined ULN. If not specified by an institution, age/sex ULN creatinine may be defined as aged >1 to <12 years, both male and female, 61.6 $\mu$mol/L; aged ≥12 to ≤16 years, both male and female, 88 $\mu$mol/L and ≥16 years female 105.6 $\mu$mol/L and ≥16 years male 114.4 $\mu$mol/L. [b]Attributed levels: patients will be considered to have elevated levels of creatinine if their probably or definitely to CTLS.

## Clinical Manifestations of TLS

### Hyperuricemia

Hyperuricemia refers to surplus of uric acid in the blood. It is defined as serum uric acid ≥8 mg/dL or 25% increase from baseline 3 days before or 7 days after initiation of chemotherapy (Cairo and Bishop, 2004). Usually developing 48 to 72 hours after therapy, it is caused by increased purine metabolism due to enhanced catabolism of nucleic acids, a consequence of increased turnover or cancer chemotherapy that aggravates cell lysis and causes rapid release of purine metabolites (Arrambide and Toto, 1993; Drakos et al., 1994). Within cells nucleic acids are catabolised to hypoxanthine, then xanthine and finally to uric acid by xanthine oxidase (see Figure 1). Uric acid clearance occurs in kidney and in normal circumstances around 500 mg of uric acid is excreted through kidneys each day (Klinenberg et al., 1965).

Usually DNA is converted into uric acid very slowly for the stability of protein-DNA complexes. This process during chemotherapy is rapid because there is huge tissue breakdown causing substantial release of DNA and RNA resulting in purine overload, followed by a noticeable rise in urate levels (Tannock, 1978). Uric acid has a pKa of 5.5 and is soluble in its ionized form at pH 7. However, the solubility of uric acid reduces with decreasing urinary pH (Wilcox, 1972).

In the renal tubules and in particular the collecting ducts the luminal pH approaches 5. At this low pH, uric acid is 13 times less soluble than at pH 7 (Klinenberg et al., 1965) and the threshold at which uric acid precipitates into crystals may be reached. Crystals obstruct urine flow in the tubules leading to obstructive uropathy (Rieselbach, 1964; Klinenberg et al., 1975; Conger et al., 1976). A uric acid: creatinine greater than 1 is indicative of uric acid nephropathy, whereas a ratio less than 0.6 to 0.75 suggests renal failure of another etiology.

Most mammals, with the exception of humans, retain their ability to convert urate to a more soluble substance called allatoin. The process is catalyzed by urate oxidase. Our inability to synthesize this enzyme is due to a point mutation in a sequence of DNA that results in a stop codon also called nonsense mutation in exon 2 of the UOX gene that occurred in our primate ancestors 15 million years ago (Oda et al., 2002).

### Hyperkalemia

It refers to excess of potassium in the bloodstream. It is

considered to be the most dangerous consequence of TLS. Potassium is the main intracellular ion regulated through the Na$^+$–K$^+$ATPase system. Its normal regulation is critical in maintaining the normal resting membrane potential of various cells: skeletal, muscle, neural and cardiac muscles (Mandal, 1997; Overgaard et al., 1997). It is defined as serum K$^+$ level ≥6 mEq/L or 25% increase from baseline 3 days before and 7 days after the initiation of therapy (Cairo and Bishop, 2004). It is suggested that due to stress on cellular metabolism in addition to chemotherapy and radiotherapy as well as reduced ATP levels may cause potassium to leak out of tumour cells before complete lysis, resulting in early elevated levels of potassium concentration in the serum. A rise in serum potassium levels is usually seen 12-24 h post-chemotherapy well before significant levels of phosphate and urate, which are reached at 48-96 h. Elevated levels of serum potassium can cause cardiac arrhythmias and lead to sudden death. Neuromuscular and cardiac tissues are most sensitive to fluctuations in K$^+$ levels. Neuromuscular symptoms may include fatigue, muscle cramps, anorexia, irritability, etc. In cardiac tissues, depending on the severity of hyperkalemia, a variety of electrocardiographic changes can occur, including peaked T wave when serum K+ level is in the range of 6-7 mEq/L, widening of QRS complex and smaller amplitude of P wave with serum K$^+$ levels varying between 7 and 8 mEq/L, fusion of QRS complex with T wave forming sine waves with serum K$^+$ levels of 8 to 9 mEq/L, and eventually atrioventricular dissociation or ventricular fibrillation and death when serum K$^+$ level goes beyond 9 mEq/L (Mandal, 1997).

*Hyperphosphatemia and hypocalcemia*

Hyperphosphatemia is defined as serum phosphate ≥4.5 mg/dL or 25% increase from baseline, and hypocalcemia as corrected calcium level ≤7 mg/dL or 25% decrease from baseline 3 days before or 7 days after starting chemotherapy (Cairo and Bishop, 2004). Both electrolyte abnormalities usually develop 24 to 48 h after chemotherapy. Hyperphosphatemia results from rapid release of intracellular phosphates into the peripheral blood during acute degradation of malignant cells, which may contain up to four times more organic and inorganic
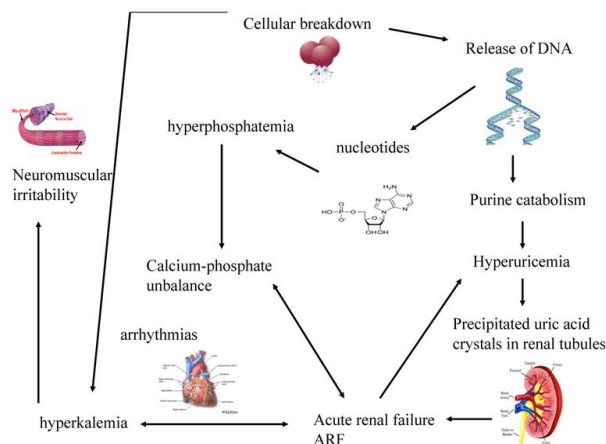
phosphates as compared to normal cells (Yarpuzlu, 2003; Davidson, 2004).

Hyperphosphatemia can lead to acute renal failure as a result of precipitation with calcium in renal tubules. The concentration of calcium in serum quickly decreases as precipitation with phosphate occurs. Precipitation of calcium phosphate occurs when the solubility product of calcium and phosphate is exceeded, leading to hypocalcemia along with organ damage associated with calcium deposition. Hypocalcemia is a metabolic disorder that is a direct consequence of hyperphosphatemia as symptoms associated with hyperphosphatemia are manifested indirectly through its effect on calcium. Hypocalcemia can result in both neurologic and cardiac symptoms. Neurologic symptoms include muscle cramps, tetany and seizures. When calcium phosphate precipitates in cardiac system serious dysrhythmias can occur. The various factors contributing to pathophysiology of tumour lysis syndrome are depicted in Figure 1.

**Incidence and risk factors**

The exact incidence of TLS is not well established. TLS is often associated with haematological malignancies (Fleming and Doukas, 1992; Hande and Garrow, 1993; Lawrence, 1994; Veenstra et al., 1994; Kadar and Krumerman, 1995; Hogan and Rosenthal, 1998) but it is also observed in various solid tumours (Mahmoud et al., 1998) with high proliferative rates and high response rate to cytotoxic therapy such as testicular cancer, breast cancer, ovarian cancer, etc. Available facts suggest that the incidence of clinical TLS is approximately 3-7% for acute leukemias and 4-11% for lymphomas (Annemans et al., 2003; Wossmann et al., 2003). However certain subgroups of leukemia patients, such as those with mature B acute lymphoblastic leukemia (ALL) and Burkitt's lymphoma/leukemia, have been reported to have a high frequency of TLS of around 25% (Stapleton et al., 1988; Montesinos et al., 2008). Table 4 summarizes the degrees of risk in

**Table 4. Risk of TLS According to Tumour Type**

| Degree of risk | Tumour type |
| --- | --- |
| High | - Burkitt's lymphoma<br>- Lymphoblastic leukemia<br>- High grade non-Hodgkin's lymphoma<br>- T-cell acute lekemia |
| Moderate | - Low grade lymphoma treated with definitive therapy<br>- Multiple myeloma<br>- Breast carcinoma treated with chemotherapy/hormonal therapy<br>- Small-cell lung carcinoma<br>- Germ-cell tumors (ovarian)<br>- Neuroblastoma |
| Low | - Hodgkin's lymphoma<br>- Low-grade lymphoma treated with interferon<br>- Medulloblastoma<br>- Merkel's cell carcinoma<br>- Adenocarcinoma of the gastrointestinal tract |

*Reproduced from Jeha (2001).



**Figure 1. Pathophysiology of Tumour Lysis Syndrome (used with permission from Cammalleri and Malaguarnera).**

patients with a particular type of cancer.

The risk of developing TLS is influenced by a number of factors including cancer mass, type of malignancy, the type and intensity of anticancer treatment, high rate of proliferation of cancer cells, sensitivity of cancer cells to anticancer therapy, and the presence of pre-existing conditions such as renal insufficiency, hypotension, etc. In general patients predisposed to developing TLS have malignancies with high rate of cell turnover and are highly sensitive to chemotherapy. The neoplastic cells associated with such malignancies are characterized by high amount of nucleic acid and phosphorus and have active purine metabolism (Ribeiro and Pui, 2002). These features are unique to certain hematologic malignancies, especially acute lymphoid leukemia and high-grade Non-Hodgkin lymphoma (NHL) (Levine, 2002). Burkitt's lymphoma has one of the highest rates of cell division among human tumours, putting patients with this particular type of NHL at the highest risk of TLS (Hecht and Aster, 2000). In patients with bulky tumour or large tumour burden (>10 cm) and highly proliferative solid tumours, there is possibility of developing spontaneous or therapy induced TLS (Jeha, 2001). In general the larger the mass of the cancer, the higher the number of cells that will lyse following anticancer therapy, the higher the risk of TLS. Cancers that are highly susceptible to therapy are more prone to cell lysis thus at a greater risk of TLS as compared to other cancers. The intensity of anticancer therapy also plays a major role in putting patients at a high risk of TLS. The more aggressive the therapy, the higher the rate of cell lysis, the greater the risk of TLS. For example, some protocols for acute lymphoblastic leukemia start with a week of prednisone monotherapy while others begin with a combination of glucocorticoid, vincristine, asparaginase and daunorubicin. A patient treated on a latter protocol would have a higher risk of TLS. Increased baseline of lactate dehydrogenase (>2 ULN) and elevated WBC counts (>25,000/$\mu$L) also contributes to the risk. A number of pre-existing conditions, such as renal insufficiency and reduced clearance of uric acid also increases the risk of TLS. A patient with pre-existing nephropathy from hypertension, diabetes, gout, etc. has a higher risk of acute kidney failure and TLS. In patient experiencing dehydration, oliguria, pre-existing hyperuricemia and acidic urine, the solubility of uric acid reduces and so does the uric acid clearance (Navolanic, 2003). Uric acid is less soluble in acidic urine and therefore crystallizes more rapidly. A patient who has acidic urine and hyperuricemia already has uric acid crystals in the renal tubules predisposing him to TLS.

## Management

### *Hydration*

Intravenous hydration should begin 24 to 48 h prior to cancer therapy and continue for 48 to 72 h after chemotherapy. Continuous infusion rates of up to 4 to 6 L/d have been suggested. Hydration increases intravascular volume and helps correct electrolyte disturbances by diluting extracellular fluid with isotonic saline, thereby reducing serum concentrations of uric acid,

phosphate and potassium (Razis et al., 1994; Lorigan et al., 1996).

### *Urinary alkalinisation*

The role of urinary alkalinisation with sodium bicarbonate is controversial (Tsokos et al., 1981). Urinary alkalinisation increases the solubility of uric acid. At physiologic pH 98% of uric acid exists in its ionized form. However in the acidic urinary filtrate environment, uric acid precipitates in the renal tubules obstructing the renal flow. Alkalinisation with sodium bicarbonate increases the solubility of uric acid by increasing the percentage of its ionized form in the urine. The goal of alkalisation should be to maintain urinary pH at 7.0-7.5. Isotonic sodium bicarbonate in 0.45% normal saline with 5% dextrose should be infused at a rate of 150-300 mL/h to achieve effective alkalisation. However alkaline pH favour precipitation of calcium phosphate crystals and can aggravate renal failure (Pak, 1969; Monbalyu et al., 1984). Therefore once hyperuricemia has been resolved, urinary alkalisation should be discontinued (Tsokos et al., 1981; Stapleton et al., 1988).

### *Treatment with allopurinol and rasburicase*

Allopurinol is a competitive inhibitor of xanthine oxidase and blocks the conversion of hypoxanthine and xanthine to uric acid (Krakoff and Meyer, 1965; Spector, 1977). Allopurinol has been established to efficiently decrease the formation of new uric acid and reduce the frequency of uric acid obstructive uropathy in patients at risk of tumour lysis syndrome (TLS). Nevertheless, allopurinol has several limitations. It only prevents the new uric acid formation, it does not reduce the amount of uric acid already present in the system. Secondly the serum levels of purine precursors, xanthine and hypoxanthine, are increased (DeConti and Calabresi, 1966; Spector, 1977). As xanthine is less soluble in urine as compared to uric acid, xanthine nephropathy resulting in acute obstructive uropathy may develop (Band et al., 1970; Landgrebe et al., 1975). Yet another drawback is that it is known to interfere with the degradation of other purines such as 6-mercaptopurine (6-MP) and azathioprine through inhibition of the p450 pathway. In general only patients
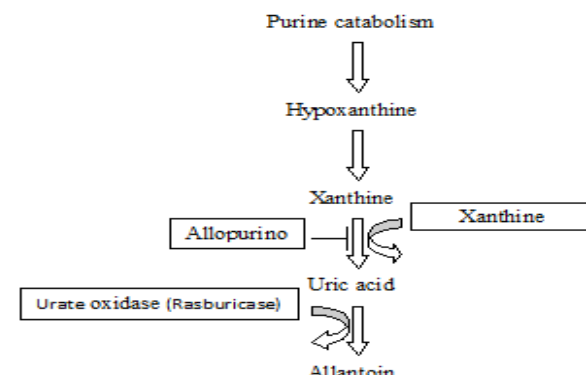


**Figure 2. Purine Catabolism Pathway.** Mode of action of rasburicase and allopurinol. Rasburicase, a recombinant form of urate oxidase, converts uric acid to allantoin. On the contrary, allopurinol, a potent inhibitor of xanthine oxidase, acts by suppressing the activity of enzyme xanthine oxidase thereby inhibiting the formation of uric acid (Hochberg and Cairo, 2008).

*Tumour Lysis Syndrome: Implications for Cancer Therapy*

who are at low risk of developing TLS are considered as suitable candidates for allopurinol prophylaxis (Cairo and Bishop, 2004; Cairo et al., 2007). This has been confirmed by a medical decision model developed by international panel of experts (Cairo and Bishop, 2004).

On the other hand, an alternative to inhibiting the action of enzyme xanthine oxidase is to promote the catabolism of uric acid to allantoin by urate oxidase as shown in Figure 2. Rasburicase is a recombinant form of urate oxidase, an enzyme not produced in humans. Rasburicase catalyses the conversion of poorly soluble uric acid into allantoin, which is five to ten times more soluble in urine as compared to uric acid and can be easily excreted by kidneys (Cheson and Dutcher, 2005; Cammalleri and Malaguarnera, 2007; Zojer and Ludwig, 2007). In general, response to rasburicase is rapid and the treatment is well tolerated (Goldman et al., 2001; Patte et al., 2002; Bosly et al., 2003; Coiffier et al., 2003). In patients at highest risk of developing TLS, rasburicase is generally recommended as the preferred prophylaxis (Cairo and Bishop, 2004; Cairo et al., 2007; Zojer and Ludwig, 2007; Mayne et al., 2008).

*Control of electrolyte disturbances*

Hyperkalemia requires aggressive management. Mild hyperkalemia (<6 mEq/L) can usually be managed with sodium polystyrene sulfonate; it should be given in the range of 50-100 g. Sodium polystyrene sulfonate is a resin that exchanges sodium for potassium in the gastrointestinal tract. Each milliequivalent of potassium is exchanged for 1 mEq of sodium. Calcium gluconate (10%) may be used for severe cardiac toxicities. Other treatment options include hypertonic glucose, insulin, loop diuretics and bicarbonate. Regular insulin at 10 U intravenously and 50 mL of 50% glucose solution over 1h will lead to potassium influx. Glucose and insulin will shift potassium from extracellular to intracellular space. Sodium bicarbonate shifts potassium intracellularly. Loop diuretics promote potassium excretion.

## Conclusions

Tumor lysis syndrome is a cluster of metabolic disturbances that usually develops during the management of various cancers such as lymphoma, leukemia and neuroblastoma. It is usually observed after initiation of chemotherapy, which results in massive destruction of tumour cells and rapid release of their contents. Late detection can result in a variety of metabolic abnormalities that manifests into life threatening complications such as renal failure, arrhythmias and seizures. Therefore early detection is vital for proper management of the disorders. This can be achieved through close monitoring of patients who are at high risk of developing the syndrome following chemotherapy. This can be done by assessment of their urine output. Levels of uric acid, lactate dehydrogenase, potassium, phosphate and calcium levels should be frequently measured. Patients may be treated with allopurinol, hydration, urinary alkalinisation or hemodialysis. Rasburicase has been established to be more effective than allupurinol because unlike allopurinol,

which prevents the formation of new uric acid but does not reduce the existing uric acid, it oxidises uric acid to a soluble product allantoin, preventing nephropathy from uric acid and xanthine. Rasburicase may revolutionize the management of TLS, as published studies show rasburicase to be a potent agent in reducing uric acid levels and preventing complications of TLS. Future studies are required to determine which patients should receive rasburicase; which dose and schedule of rasburicase is most effective for treatment; which patients only require allopurinol to alleviate the symptoms; can allopurinol and rasburicase be used successively used for treatment. Answers to these questions and a lot more require further studies to reduce the possibility of cancer patients becoming victims of metabolic disorders.

## Acknowledgement

## References

Annemans L, Moeremans K, Lamotte M, et al (2003). 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*, **44**, 77-83.

Arrambide K, Toto RD (1993). Tumor lysis syndrome. *Semin Nephrol*, **13**, 273-80.

Band PR, Silverberg DS, Henderson JF, et al (1970). Xanthine nephropathy in a patient with lymphosarcoma treated with allopurinol. *N Engl J Med*, **283**, 354-7.

Bosly A, Sonet A, Pinkerton CR, et al (2003). Rasburicase (recombinant urate oxidase) for the management of hyperuricemia in patients with cancer: report of an international compassionate use study. *Cancer*, **98**, 1048-54.

Cairo MS, Bishop M (2004). Tumour lysis syndrome: new therapeutic strategies and classification. *Br J Haematol*, **127**, 3-11.

Cairo M S, Coenelis M, Baruchel A, et al (2007). Risk assessment and medical decision model for prophylaxis and treatment of hyperuricemia and tumor lysis syndrome (TLS): international expert panel analysis. *J Clin Oncol*, **25**, 17006.

Cammalleri L, Malaguarnera M (2007). Rasburicase represents a new tool for hyperuricemia in tumor lysis syndrome and in gout. *Int J Med Sci*, **4**, 83-93.

Cheson B D, Dutcher B S (2005). Managing malignancy-associated hyperuricemia with rasburicase. *J Support Oncol*, **3**, 117-24.

Conger J D, Falk S A, Guggenheim S J, Burke T J (1976). A micropuncture study of the early phase of acute urate nephropathy. *J Clin Invest*, **58**, 681-9.

Coiffier B, Mounier N, Bologna S, et al (2003). Efficacy and safety of rasburicase (recombinant urate oxidase) for the prevention and treatment of hyperuricemia during induction chemotherapy of aggressive non-Hodgkin's lymphoma: results of the GRAAL1 (Groupe d'Etude des Lymphomes de l'Adulte Trial on Rasburicase Activity in Adult Lymphoma) study. *J Clin Oncol*, **21**, 4402-6.

Davidson M B, Thakkar S, Hix J K, et al (2004). Pathophysiology, clinical consequences and treatment of tumour lysis syndrome. *Am J Med*, **116**, 546-4.

DeConti R C, Calabresi P (1966). Use of allopurinol for prevention and control of hyperuricemia in patients with

*Denish Mika et al*

neoplastic disease. *N Engl J Med*, **274**, 481-6.

Del Toro G, Morris E, Cairo M S (2005). Tumor lysis syndrome: pathophysiology, definition, and alternative treatment approaches. *Clin Adv Hematol Oncol*, **3**, 54-61.

Drakos P, Bar-Ziv J, Catane R (1994). Tumor lysis syndrome in nonhematologic malignancies. Report of a case and review of the literature. *Am J Clin Oncol*, **17**, 502-5.

Fleming D R, Doukas M A (1992). Acute tumor lysis syndrome in hematologic malignancies. *Leuk Lymphoma*, **8**, 315-8.

Goldman S C, Holcenberg J S, Finklestein J Z, et al (2001). A randomized comparison between rasburicase and allopurinol in children with lymphoma or leukemia at high risk for tumor lysis. *Blood*, **97**, 2998-3003.

Hande K R, Garrow G C (1993). Acute tumor lysis syndrome in patients with high-grade non-Hodgkin's lymphoma. *Am J Med*, **94**, 133-9.

Hecht J L, Aster J C (2000). Molecular biology of Burkitt's lymphoma. *J Clin Oncol*, **18**, 3707-21.

Hijiya N, Metzger M L, Pounds S, et al (2005). Severe cardiopulmonary complications consistent with systemic inflammatory response syndrome caused by leukemia cell lysis in childhood acute myelomonocytic or monocytic leukemia. *Pediatr Blood Cancer*, **44**, 63-9.

Hochberg J, Cairo M S (2008). Tumor lysis syndrome: current perspective. *Haematologica*, **93**, 67-74.

Hogan D K, Rosenthal L D (1998). Oncologic emergencies in the patient with lymphoma. *Semin Oncol Nurs*, **14**, 312-20.

Jeha S (2001). Tumor lysis syndrome. *Semin Hematol*, **38**, 4-8.

Kadar N, Krumerman M (1995). Possible metaplastic origin of lymph node "metastases" in serous ovarian tumor of low malignant potential (borderline serous tumor). *Gynecol Oncol*, **59**, 394-7.

Klinenberg J R, Goldfinger S, Seegmiller J E (1965). The effectiveness of the xanthine oxidase inhibitor allopurinol in the treatment of gout. *Ann Intern Med*, **62**, 639-47.

Klinenberg J R, Kippen I, Bluestone R (1975). Hyperuricemic nephropathy: pathologic features and factors influencing urate deposition. *Nephron*, **14**, 88-98.

Krakoff I H, Meyer R L (1965). Prevention of hyperuricemia in leukemia and lymphoma: use of allopurinol, a xanthine oxidase inhibitor. *JAMA*, **193**, 1-6.

Lawrence J (1994). Critical care issues in the patient with hematologic malignancy. *Semin Oncol Nurs*, **10**, 198-207.

Landgrebe A R, Nyhan W L, Coleman M (1975). Urinary-tract stones resulting from the excretion of oxypurinol. *N Engl J Med*, **292**, 626-7.

Levine A M (2002). Challenges in the management of Burkitt's lymphoma. *Clin Lymphoma*, **3**, 19-25.

Lorigan P C, Woodings P L, Morgenstern G R, Scarffe J H (1996). Tumour lysis syndrome, case report and review of the literature. *Ann Oncol*, **7**, 631-6.

Mahmoud H H, Leverger G, Patte C, Harvey E, Lascombes F (1998). Advances in the management of malignancy-associated hyperuricaemia. *Br J Cancer*, **77**, 18-20.

Mandal A K (1997). Hypokalemia and hyperkalemia. *Med Clin North Am*, **81**, 611-39.

Mayne N, Keady S, Thacker M (2008). Rasburicase in the prevention and treatment of tumour lysis syndrome. *Intensive Crit Care Nurs*, **24**, 59-62.

Monbalyu J, Zachee P, Verberckmoes R, Boogaerts MA (1984). Transient acute renal failure due to tumor-lysis-induced severe phosphate load in a patient with Burkitt's lymphoma. *Clin, Nephrol*, **22**, 47-50.

Montesinos P, Lorenzo I, Martín G, et al (2008). Tumor lysis syndrome in patients with acute myeloid leukemia: identification of risk factors and development of a predictive model. *Haematologica*, **93**, 67-74.

Nakamura M, Oda S, Sadahiro T, et al (2009). The role of hypercytokinemia in the pathophysiology of tumor lysis syndrome (TLS) and the treatment with continuous hemodiafiltration using a polymethylmethacrylate membrane hemofilter (PMMA-CHDF). *Transfus Apher Sci*, **40**, 41-7.

Navolanic P M, Pui C H, Larson R A, et al (2003). Elitek-rasburicase: an effective means to prevent and treat hyperuricemia associated with tumor lysis syndrome, a Meeting Report, Dallas, Texas, January 2002. *Leukemia*, **17**, 499-514.

Oda M, Satta Y, Takenaka O, Takahata N (2002). Loss of urate oxidase activity in hominoids and its evolutionary implications. *Mol Biol Evol*, **19**, 640-53.

Overgaard K, Nielsen O B, Clausen T (1997). Effects of reduced electrochemical $Na^+$ gradient on contractility in skeletal muscle: role of the $Na^+$-$K^+$ pump. *Pflugers Arch*, **434**, 457-65.

Pak C Y (1969). Physicochemical basis for formation of renal stones of calcium phosphate origin: calculation of the degree of saturation of urine with respect to brushite. *J Clin Invest*, **48**, 1914-22.

Patte C, Sakiroglu C, Ansoborlo S, et al (2002). Urate-oxidase in the prevention and treatment of metabolic complications in patients with B-cell lymphoma and leukemia, treated in the Société Française d'Oncologie Pédiatrique LMB89 protocol. *Ann Oncol*, **13**, 789-95.

Razis E, Arlin Z, Ahmed T (1994). Incidence and treatment of tumour lysis syndrome in patients with acute leukaemia. *Acta Haematol*, **91**, 171-4.

Ribeiro R C, Pui C H (2002). Hyperuricemia in patients with cancer. *Am J Cancer*, **1**, 409-22.

Rieselbach R E, Bentzel C J, Cotlove E, et al (1964). Uric acid excretion and renal function in the acute hyperuricemia of leukemia: pathogenesis and therapy of uric acid nephropathy. *Am J Med*, **37**, 872-83.

Spector T (1977). Inhibition of urate production by allopurinol. Biochem. *Pharmacol*, **26**, 355-8.

Soares M, Feres G A, Salluh J I (2009). Systemic inflammatory response syndrome and multiple organ dysfunction in patients with acute tumor lysis syndrome. *Clinics (Sao Paulo)*, **64**, 479-81.

Stapleton F B, Strother D R, Roy S, et al (1988). Acute renal failure at onset of therapy for advanced stage Burkitt lymphoma and B cell acute lymphoblastic lymphoma. *Pediatrics*, **82**, 863-9.

Tannock I (1978). Cell kinetics and chemotherapy: a critical review. *Cancer Treat Rep*, **62**, 1117-33.

Tsokos G C, Balow J E, Spiegel R J, Magrath I T (1981). Renal and metabolic complications of undifferentiated and lymphoblastic lymphomas. *Medicine (Baltimore)*, **60**, 218-29.

Veenstra J, Krediet R T, Somers R, Arisz L (1994). Tumour lysis syndrome and acute renal failure in Burkitt's lymphoma. Description of 2 cases and a review of the literature on prevention and management. *Neth J Med*, **45**, 211-6.

Wossmann W, Schrappe M, Meyer U, Zimmermann M, Reiter A (2003). Incidence of tumor lysis syndrome in children with advanced stage Burkitt's lymphoma/leukemia before and after introduction of prophylactic use of urateoxidase. *Ann Hematol*, **82**, 160-5.

Wilcox W R, Khalaf A, Weinberger A, Kippen I, Klinenberg J R (1972). Solubility of uric acid and monosodium urate. *Med Biol Eng*, **10**, 522-31.

Yarpuzlu A A (2003). A review of clinical and laboratory findings and treatment of tumor lysis syndrome. *Clin Chim Acta*, **333**, 13-8.

Zojer N, Ludwig H (2007). Hematological emergencies. *Ann Oncol*, **18**, 45-8.