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CORE TRAINING FOR DOCTORS

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Tumour lysis syndrome

Introduction

Tumour lysis syndrome is a group of metabolic abnormalities that result from the rapid release of intracellular metabolites such as nucleic acids, proteins, phosphorus and potassium from lysed malignant cells. This process can potentially cause hyperuricaemia, hyperkalaemia, hyperphosphataemia, with or without hypocalcaemia and uraemia, that can lead to renal failure, arrhythmias, seizures and even death. This article discusses the diagnostic and management aspects of the syndrome.

Definition

Laboratory tumour lysis syndrome is defined as either a 25% change or level above or below normal, as defined below, for any two or more serum values of uric acid, potassium, phosphate and corrected calcium within 3 days before or 7 days after the initiation of chemotherapy (*Table 1*). This assumes that a patient has or will receive adequate hydration and a hypouricaemic agent.

Clinical tumour lysis syndrome requires the laboratory evidence of metabolic changes and significant clinical toxicity that requires clinical intervention. Clinical tumour lysis syndrome is defined as the presence of laboratory tumour lysis syndrome and any one or more of the criteria below which should not be directly or probably attributable to a therapeutic agent:

1. Creatinine: ≥1.5 times the upper limit of normal (age >12 years or age adjusted)
2. Cardiac arrhythmia or sudden death
3. Seizure.

Malignancies that can cause tumour lysis syndrome are listed in *Table 2*.

Table 1. Definition of laboratory tumour lysis syndrome

Uric acid	≥476 umol/litre or 25% increase from baseline
Potassium	≥6 mmol/litre or 25% increase from baseline
Phosphorous	≥2.1 mmol/litre (children), ≥1.45 mmol/litre (adults) or 25% increase from baseline
Corrected calcium	≤1.75 mmol/litre or 25% decrease from baseline

From Cairo and Bishop (2004)

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Pathophysiology

While tumour lysis syndrome may occur spontaneously before treatment, it is commonly observed 12–72 hours after cytotoxic chemotherapy. The initiation of treatment often results in the rapid release of intracellular anions, cations and the metabolic products of proteins and nucleic acids into the bloodstream. This is summarized in *Figure 1* and *Table 3*.

Clinical impact of tumour lysis syndrome

Clinical manifestations are caused by the metabolic abnormalities and include nausea, vomiting, lethargy, oedema, fluid overload, congestive heart failure, cardiac dysrhythmias, seizures, muscle cramps, tetany, syncope and possibly sudden death.

Table 2. Malignancies that can cause tumour lysis syndrome

Most common	Acute lymphoblastic leukaemia
	High grade non-Hodgkin's lymphoma, in particular Burkitt's lymphoma
Less common	Chronic lymphocytic leukaemia
	Acute myeloid leukaemia
	Plasma cell disorders
Anecdotal	Low grade and intermediate grade non-Hodgkin's lymphoma
	Hodgkin's lymphoma
	Chronic myeloid leukaemia in blast crisis
	Myeloproliferative disorders
	Testicular cancer
	Breast cancer
	Small cell lung cancer

From Cairo and Bishop (2004)

Risk stratification

As reported by Cairo et al (2010), risk factors for tumour lysis syndrome include age, type of malignancy, tumour burden (stage or lactate dehydrogenase level), white blood cell counts and whether renal function is compromised. These have been collated into a comprehensive risk classification model in *Table 4*. According to this model, low risk disease was defined as a risk of less than 1% of developing tumour lysis syndrome, intermediate risk disease was defined as a risk of 1–5% and high risk disease was defined as a risk of greater than 5%.

Management

The principal feature in the management of acute tumour lysis syndrome is having a high index of suspicion, identifying patients at high risk and aggressively instituting prophylaxis. Tumour therapy should be delayed, if possible, in patients at high risk of tumour lysis syndrome until prophylaxis is initiated. Unfortunately, a delay in therapy is not possible for many, because of the aggressive nature of their malignancy. In this situation, clinical judgment should prevail. Regardless of time constraints the patient should have reliable venous access and be treated in an intensive care or haematology/oncology unit with personnel who are trained and familiar with the complications associated with tumour lysis syndrome.

Prophylaxis

According to Cairo et al (2010), patients with a low risk of developing tumour lysis syndrome should be monitored; normal hydration and no prophylaxis for hyperuricaemia should be given except in cases of signs of metabolic changes, bulky and/or advanced disease and/or high proliferative disease, in which case allopurinol should be added.

Patients with an intermediate risk of developing tumour lysis syndrome should be monitored, given increased hydration (3 litres/m^2/day or 200 ml/kg/day if <10 kg) and a urine output of ≥100 ml/m^2/hour (3 ml/kg/hour if <10 kg) should be maintained. Despite adequate hydration, diuretics may be required if there is no evidence of acute obstructive uropathy and/or hypovolaemia to maintain a urine output of ≥100 ml/m^2/hour (≥3 ml/kg/hour if <10 kg). Such diuretics may include furosemide (0.5–1.0 mg/kg). In the event of severe oliguria or anuria, a single dose of furosemide (2–4 mg/kg) may be considered to improve or initiate urinary output. Potassium, calcium and phosphate should not be initially added to hydration fluids so as to avoid hyperkalaemia, hyperphosphataemia and/or calcium phosphate precipitation. Alkalinization can lead to the formation of xanthine crystals and obstructive uropathy and is generally not recommended. Allopurinol should be administered.

In patients with high risk of developing tumour lysis syndrome, frequent monitoring should be performed, increased hydration should be given (3 litres/m^2/day) (unless evidence of renal insufficiency and oliguria) and rasburicase (0.1–0.2 mg/kg) should be administered.

The above recommendations are summarized in *Table 5*.

Figure 1. Pathophysiology and clinical features of tumour lysis syndrome.

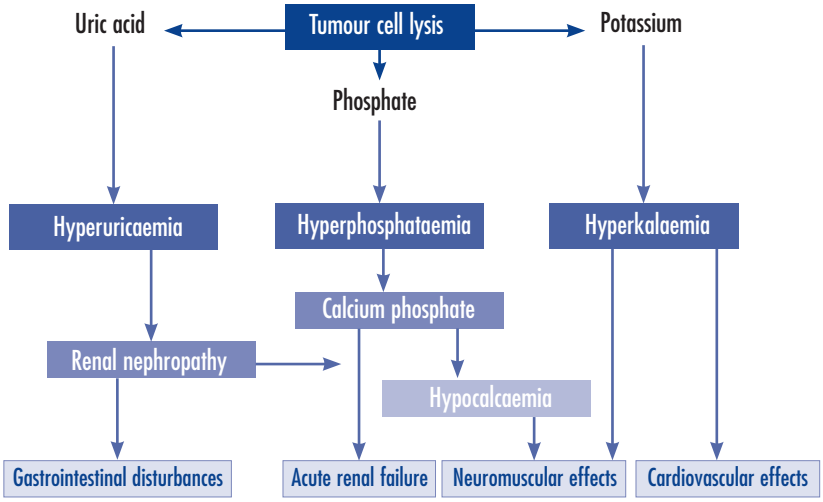

Table 3. Pathophysiological mechanisms of laboratory abnormalities in tumour lysis syndrome

Abnormality	Mechanism
Hyperuricaemia	Catabolism of intracellular purine nucleic acids to hypoxanthine, xanthine and finally uric acid by xanthine oxidase
Hyperphosphataemia	Rapid release of intracellular phosphorus from malignant cells
	Exacerbated by uric acid nephropathy
Hyperkalaemia	Rapid release of potassium from malignant cells
	Exacerbated by acute renal failure and iatrogenic administration of potassium
Hypocalcaemia	Caused by hyperphosphataemia and tubular precipitation of calcium phosphate
Uraemia	Caused by uric acid nephropathy and calcium phosphate deposition in tubules

From Cairo and Bishop (2004)

Hypouricaemic agents

The two drugs used are allopurinol and rasburicase.

Allopurinol

Allopurinol is a xanthine analogue that, when converted in vivo to oxypurinol, is a competitive inhibitor of xanthine oxidase which inhibits the metabolism of xanthine and hypoxanthine to uric acid. Allopurinol effectively decreases the formation of new uric acid and reduces the incidence of uric acid obstructive uropathy in patients at risk of tumour lysis syndrome.

However, allopurinol has several limitations that require consideration:

1. It does not reduce uric acid produced before allopurinol initiation
2. Serum levels of the purine precursors, xanthine and hypoxanthine, are

Table 4. Risk stratification

Low risk	Most solid tumours	
	Multiple myeloma	
	Chronic myeloid leukaemia	
	Indolent non-Hodgkin's lymphoma	Small lymphocytic
		Follicular
		Marginal zone B cell
		Mucosal-associated lymphoid tissue
		Mantle cell (non-blastoid variants)
		Cutaneous T cell
		Hodgkin's lymphoma
	Chronic lymphocytic leukaemia treated with alkylating agents	
	Acute myeloid leukaemia and white blood cell count 25 x 10^9/litre and lactate dehydrogenase < 2 x upper limit of normal	
	Adult intermediate grade* non-Hodgkin's lymphoma and normal lactate dehydrogenase	
	Adult anaplastic large cell lymphoma	
Intermediate risk	Acute myeloid leukaemia with white blood cell count 25–100 x 10^9/litre	
	Acute myeloid leukaemia and white blood cell count <25 x 10^9/litre and lactate dehydrogenase ≥ 2 x upper limit of normal	
	Adult intermediate grade* non-Hodgkin's lymphoma and lactate dehydrogenase > upper limit of normal and non-bulky disease	
	Chronic lymphocytic leukaemia treated with fludarabine, rituximab or other targeted/biological therapies and/or those with high white blood cell count (≥50 x 10^9/litre)	
	Childhood anaplastic large cell lymphoma stage III/IV	
	Childhood intermediate grade* non-Hodgkin's lymphoma stage III/IV with lactate dehydrogenase < 2 x upper limit of normal	
	Acute lymphoblastic leukaemia and white blood cell count <100 x 10^9/litre and lactate dehydrogenase < 2 x upper limit of normal	
	Lymphoblastic lymphoma stage I/II and lactate dehydrogenase < 2 x upper limit of normal	
	Burkitt's lymphoma with lactate dehydrogenase < 2 x upper limit of normal	
	Burkitt's leukaemia	
	Neuroblastoma, germ cell tumours and small cell lung cancer	
	Solid tumours with bulky† or advanced stage disease	
	Low risk disease with renal dysfunction and/or renal involvement	
High risk	Acute myeloid leukaemia and white blood cell count ≥100 x 10^9/litre	
	Acute lymphoblastic leukaemia and white blood cell count ≥100 x 10^9/litre and/or lactate dehydrogenase ≥ 2 x upper limit of normal	
	Adult intermediate grade* non-Hodgkin's lymphoma and lactate dehydrogenase > upper limit of normal and bulky disease†	
	Burkitt's lymphoma stage III/IV and/or lactate dehydrogenase ≥ 2 x upper limit of normal	
	Lymphoblastic lymphoma stage III/IV and/or lactate dehydrogenase ≥ 2 x upper limit of normal	
	Intermediate risk disease with renal dysfunction and/or renal involvement	
	Intermediate risk disease with uric acid, potassium and/or phosphate > upper limit of normal	

*Intermediate grade non-Hodgkin's lymphoma includes adult T cell lymphoma, diffuse large B cell lymphoma, peripheral T cell lymphoma, transformed lymphoma and mantle cell lymphoma (blastoid variants). †Bulky disease is defined as mass >10 cm. From Cairo et al (2010)

increased. As xanthine is less soluble in urine in comparison with uric acid, xanthine nephropathy resulting in acute obstructive uropathy may develop

3. Allopurinol reduces the degradation of other purines, including 6-mercaptopurine and azathioprine. A dose reduction of 50–70% of each of these purines, especially 6-mercaptopurine, is recommended during concomitant use with allopurinol.

Rasburicase

Rasburicase is recombinant urate oxidase. The gene encoding urate oxidase has now been cloned from *Aspergillus flavus* and expressed in a modified strain of *Saccharomyces cerevisiae*, allowing production and purification of the recombinant enzyme (rasburicase), potentially reducing the risk of contaminant-related allergic reactions. It promotes the catabolism of uric acid to allantoin by urate oxidase. In comparison with uric acid, allantoin is five to ten times more soluble in urine. It is initially given for one dose and repeated if clinically necessary. The average duration of therapy is 2 days but can vary from 1–7 days.

Table 6 summarizes key points regarding administration of hypouricaemic agents.

Management of established tumour lysis syndrome

Despite appropriate preventive measures, approximately 3–5% of patients develop laboratory and/or clinical tumour lysis syndrome. Patients who develop tumour lysis syndrome should receive intensive supportive care with continuous cardiac monitoring and measurement of electrolytes, creatinine

Table 5. Tumour lysis syndrome prophylaxis recommendation based on tumour lysis syndrome risk

Low risk	Monitoring
	Hydration
	+/- Allopurinol
Intermediate risk	Monitoring
	Hydration
	Allopurinol
High risk	Monitoring
	Hydration
	Rasburicase

From Cairo et al (2010)

and uric acid every 4–6 hours. Effective management involves treating specific electrolyte abnormalities (*Table 7*), the use of rasburicase with repeated doses as necessary, hydration with or without a loop diuretic, and the appropriate use of renal replacement therapy. Early consultation with an expert in renal medicine is advisable.

Conclusions

Tumour lysis syndrome is a constellation of metabolic derangements secondary to tumour lysis that overrides normal physiological pathways. Humans are especially vulnerable to developing tumour lysis syndrome because of the lack of the presence of urate oxidase to convert uric acid to allantoin.

Successful prevention of tumour lysis syndrome depends on the prompt identification of clinical and laboratory characteristics, signs and symptoms of patients at risk. The risk classification model, developed by a panel of tumour lysis syndrome experts, integrates diverse criteria into a user-friendly clinical tool for physicians who frequently see patients at risk for tumour lysis syndrome.

Establishment of vascular access and the initiation of prophylactic measures, especially hydration and administration of allopurinol or rasburicase, are vital. The management of established tumour lysis syndrome involves close monitoring, aggressive hydration, treatment of electrolyte abnormalities, use of rasburicase and appropriate renal replacement therapy. BJHM

KEY POINTS

- Tumour lysis syndrome is a life-threatening oncological emergency that occurs as a result of tumour breakdown, following the initiation of cytotoxic therapy or spontaneously.
- It is characterized by hyperuricaemia, hyperkalaemia, hyperphosphataemia, with or without hypocalcaemia and uraemia, that can lead to renal failure, arrhythmias, seizures and even death.
- The key features in managing tumour lysis syndrome are having a high index of suspicion, risk stratification and aggressively instituting prophylaxis.
- Essential components of management are aggressive hydration, control of hyperuricaemia with rasburicase and allopurinol, close monitoring and treatment of electrolyte abnormalities and renal replacement therapy, if required.

Conflict of interest: none.

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Coiffier B, Altman A, Pui CH, Younes A, Cairo MS (2008) Guidelines for the management of pediatric and adult tumor lysis syndrome: an evidence-based review. *J Clin Oncol* **26**(16): 2767–78

Table 6. Administration of hypouricaemic agents

Allopurinol	100 mg/m^2/dose every 8 hours (10 mg/kg/day divided every 8 hours) per orally (maximum 800 mg/day) or 200–400 mg/m^2/day in 1–3 divided doses; intravenously (maximum 600 mg/day)
	Reduce dose by 50% or more in renal failure
	Reduce 6-mercaptopurine and/or azathioprine doses by 65–75% with concomitant allopurinol
	Adjust doses of drugs metabolized by P450 hepatic microsomal enzymes with concomitant allopurinol
Rasburicase	Contraindicated in glucose-6-phosphate dehydrogenase-deficient patients and pregnant or lactating women
	0.05–0.20 mg/kg intravenously over 30 minutes
	To measure uric acid levels place blood sample immediately on ice to avoid continual pharmacological ex vivo enzymatic degradation
	10% incidence of antibody formation. There is concern that subsequent administration could enhance hypersensitization or limit the clinical effect

From Coiffier et al (2008)

Table 7. Management of electrolyte abnormalities

Hyperphosphataemia	Moderate (≥2.1 mmol/litre in children or ≥1.45 mmol/litre in adults)	Avoid intravenous phosphate administration
		Aluminium hydroxide orally 15 ml (50–150 mg/kg/24 h) 6-hourly
	Severe	Renal replacement therapy, e.g. dialysis
Hypocalcaemia (≤1.75 mmol/litre)	Asymptomatic	No therapy
	Symptomatic	Calcium gluconate 50–100 mg/kg intravenously (increases risk of calcium phosphate deposition and obstructive uropathy)
Hyperkalaemia	Moderate and asymptomatic (≥6.0 mmol/litre)	Avoid intravenous and oral potassium
		Electrocardiogram and cardiac rhythm monitoring
		Sodium polystyrene sulphonate
	Severe (≥7.0 mmol/litre) and/or symptomatic	Same as for moderate and asymptomatic cases, plus
		Calcium gluconate (100–200 mg/kg) intravenously and/or
		Regular insulin (0.1 unit/kg intravenously) + 25% dextrose (2 ml/kg) intravenously
		Dialysis
Renal dysfunction (uraemia)	Fluid and electrolyte management	
	Uric acid and phosphate management	
	Adjust renally excreted drug doses	
	Renal replacement therapy, e.g. dialysis	

From Coiffier et al (2008)