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The clinical management of tumour lysis syndrome in haematological malignancies

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Summary

Tumour lysis syndrome (TLS) is caused by the disintegration of malignant cells, usually following the instigation of chemotherapy, although it may already be established at the time of initial presentation in a minority of cases. As a direct consequence of malignant cell breakdown, intracellular ions, proteins, nucleic acids and their metabolites are released into the plasma causing the characteristic metabolic abnormalities of TLS; hyperuricaemia, hyperkalaemia, hyperphosphataemia and hypocalcaemia. In many cases the release of large amounts intracellular contents is so abrupt that the normal homeostatic mechanisms are rapidly overwhelmed and without prompt, effective management, the clinical effects of TLS soon become apparent.

Keywords: tumour lysis, hyperuricaemia, allopurinol, rasburicase, haematological malignancy.

First described in 1929 in adults with chronic leukaemia who had undergone radiotherapy (Bedrna & Polcák, 1929), tumour lysis syndrome (TLS) is now a well recognized haematological emergency with potentially severe consequences including acute renal failure, cardiac arrhythmias, seizures and even death. Both adult and paediatric groups are affected. Although mostly seen in the first few days after the initiation of cytotoxic chemotherapy, TLS has also been observed in haematological malignancies after radiotherapy (Yamazaki *et al*, 2004), steroids (Sparano *et al*, 1990; Coutinho *et al*, 1997) and immunotherapy (Yang *et al*, 1999), and rarely as spontaneous TLS (Jasek & Day, 1994).

Over the last two decades the development of an accepted system of definition and classification of TLS has significantly improved the understanding of the aetiology and incidence of TLS in different patient groups (Hande & Garrow, 1993; Cairo & Bishop, 2004). Furthermore, with the development of increasingly effective therapy to counteract the effects of hyperuricaemia, the same system can be utilized to allocate appropriate prophylactic treatment regimens to individual patients presenting with malignancy, thus avoiding over treatment and the inappropriate use of the expensive but extremely effective enzyme, recombinant urate oxidase (rasburicase).

The primary aim of the management of TLS is to increase the urinary excretion of potassium and phosphate ions and uric acid. In most patients this can be achieved by ensuring a high fluid intake and the use of uricosuric drugs. If this fails, crystallization of uric acid and calcium phosphate in the renal tubules leads to reduced renal excretion of potassium with consequent worsening of plasma hyperkalaemia, which, alone or in tandem with the effects of associated hypocalcaemia, may cause cardiac arrhythmias and even sudden death. (Fig 1).

Because the instigation of treatment for the underlying malignancy will inevitably cause an acceleration of tumour cell disintegration with potential worsening of TLS, chemotherapy should ideally not be started until the measures put in place to control TLS have had sufficient time to be effective. For most patients with haematological malignancy this will entail a delay of 24–48 h. However, such a delay in chemotherapy might not be advisable for patients presenting with the most aggressive tumours. For these patients treatment with recombinant urate oxidase can often permit chemotherapy regimens to be started within a few hours (see below).

Incidence of tumour lysis syndrome

The incidence of TLS is extremely variable and disease-dependent (Table I). TLS is more likely to develop in tumours with high tumour burden, rapid cell turnover and increased sensitivity to chemotherapeutic agents and so is most often seen in acute leukaemias with high white cell counts at presentation and diffuse Burkitt-type non-Hodgkin lymphoma. However in other cases, TLS can occur unexpectedly in apparently low risk patients and vigilance is required in all patients presenting with malignancy particularly during the

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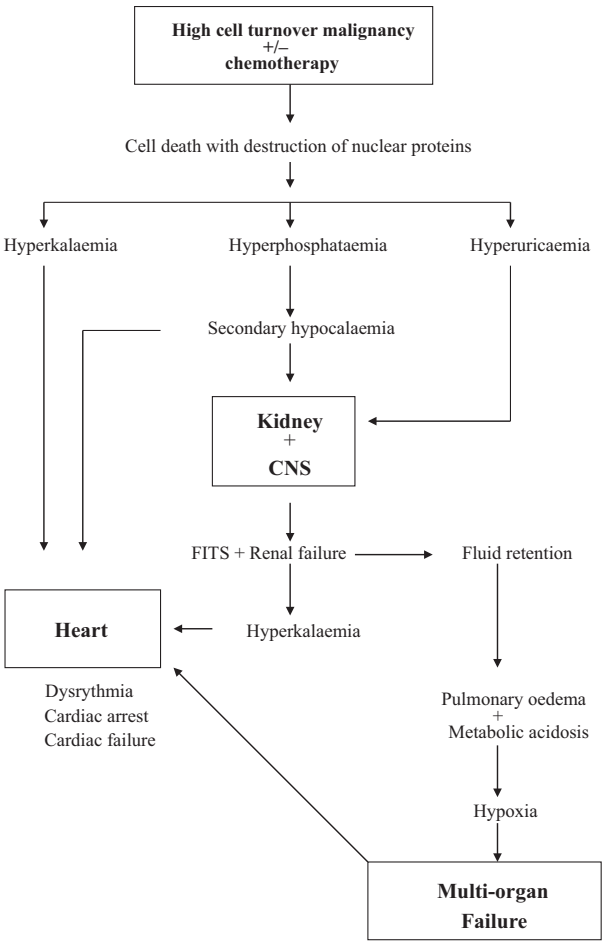

Fig 1. The pathogenesis of tumour lysis syndrome.

first week after the instigation of their treatment (List *et al*, 1990; McCroskey *et al*, 1990; Yang *et al*, 1999). Historical data are unreliable because, as the prophylactic management of TLS has improved, its incidence has reduced and so statistical data concerning the occurrence of TLS derived from past medical literature has become less relevant.

The German Berlin-Frankfürt-Münster (BFM) group reported over 11 years of experience of 1791 children with non-Hodgkin lymphoma (NHL) enrolled on the NHL-BFM 90 and 95 protocols (Wössmann *et al*, 2003); 4·4% of all the patients developed TLS and 2·3% anuria, of which 85% of the TLS cases and 83% of the anuric patients came from the Burkitt lymphoma and B-cell acute lymphoblastic leukaemia (B-ALL) subgroup, which made up only 44% of the total number of patients in the trials. The highest incidences of TLS (26·4%) and of anuria (14·1%) were seen in the B-ALL patients. While the incidence of TLS is highest in Burkitt lymphoma, in terms of numbers, most cases in children occur with high white cell T and B precursor ALL.

A more recent study of 772 patients over 13 years of age with acute myeloid leukaemia (Montesinos *et al*, 2008) reported an incidence of 12% of patients with TLS and 5% with clinical TLS (CTLS). In 19 of the 772 patients (2%), CTLS was considered to be the major cause of death (Montesinos *et al*, 2008).

The use of urate oxidase prophylaxis has significantly altered the clinical situation. The reports of three international studies using the same chemotherapy regimen for Burkitt lymphoma and B-ALL reported contrasting results with reference to the need for renal dialysis at induction; the French group used non-recombinant urate oxidase (uricozyme) and reported a rate of 1·7% (Patte *et al*, 2002) whereas data from the UK and US groups, which reported earlier and did not use urate oxidase therapy, had dialysis rates of 14·3% and 21%, respectively (Bowman *et al*, 1996; Atra *et al*, 1998). Similar results were described in the BFM study described above (Wössmann *et al*, 2003). The 11 year study was split into three periods; Period 1 during which no urate oxidase was given, Period 2 where some patients received it and Period 3 during which all 'high risk' patient should have received urate oxidase. In the highest risk group, which included patients with B-cell ALL, the incidence of TLS and anuria reduced from 20·5% and 14·4% in Period 1 respectively to 9·4% and 3·8% in Period 3.

Aetiology

The rapid release of nucleic acids, proteins and intracellular metabolites from tumour cells overwhelms the normal homeostatic control mechanisms and leads directly to increases of plasma uric acid, phosphate, potassium and a reduction in plasma calcium (Locatelli & Rossi, 2005). In the majority of cases of TLS, these abnormalities occur as a consequence of the initiation of treatment for cancers with a high tumour burden, a high rate of cell turnover and an increased sensitivity to antimitotic agents. Other factors may also increase the risk of developing TLS. These include elevated serum lactate dehydrogenase (LDH), extensive bone marrow involvement, pre-existing renal disease or reduced urinary output (Ribiero & Pui, 2003; Davidson *et al*, 2004). TLS may also be more common in elderly patients (Locatelli & Rossi, 2005). However, in a minority of patients the metabolic derangements are already present before the start of treatment, most often in patients with B-cell NHL and mature B-cell leukaemia (Jasek & Day, 1994; Alkhuja & Ulrick, 2002; Hsu *et al*, 2004). In others, TLS can develop unexpectedly in patients presenting with apparently low TLS-risk malignancies.

Hyperuricaemia

Hyperuricaemia is a direct consequence of the catabolism of nucleic acids released by the disintegration of the malignant cells (Fig 1). If unchecked, the normal homeostatic metabolic pathways soon fail with a build up of uric acid that crystallizes out as urate, particularly in the relatively acid environment of the distal renal tubules. The urate crystals physically block the renal tubules causing acute renal failure. If not already existent at presentation, hyperuricaemia most often develops 48–72 h after the start of chemotherapy (Locatelli & Rossi, 2005).

Table I. Risk stratification for haematological malignancies at initial assessment pre- chemotherapy (adapted from Cairo *et al*, 2010).

	Risk category		
Malignancy	Low*	Intermediate	High
NHL	Indolent NHL		
	Adult ALCL	Childhood ALCL stage III/IV	
	Adult intermediate grade NHL + LDH < 2 × ULN	Adult intermediate grade NHL + LDH > 2 × ULN	
	LL stage I/II + LDH < 2 × ULN	LL stage III/IV or LDH > 2 × ULN	
	N/A	Childhood intermediate grade NHL	
	N/A	Burkitt lymphoma + LDH < 2 × ULN	Burkitt lymphoma stage III/IV or LDH > 2 × ULN
Hodgkin Lymphoma	Most patients*		
ALL	N/A	WBC < 100×10^9/l + LDH < 2 × ULN	WBC > 100×10^9/l or LDH > 2 × ULN
AML	WBC < 25×10^9/l + LDH < 2 × ULN	WBC 25-100×10^9/l or WBC < 25×10^9/l + LDH > 2 × ULN	WBC > 100×10^9/l
CLL	Most patients, unless:	Treated with Fludarabine/Rituximab or WBC > 50×10^9/l	
CML	Most patients, unless:	Accelerated blast crisis	
Multiple myeloma	Most patients*		

Additional risk factors: Tumour Burden: Bulky disease (>10 cm), LDH >2 × ULN; Renal Function: Oliguria, Pre-existing renal failure; Baseline Uric Acid: >450 μmol/l; Increased tumour cell turnover and/or exquisite sensitivity to chemotherapy; and Already evidence of pre-treatment TLS at presentation.

NHL, non-Hodgkin Lymphoma; ALCL, Anaplastic large cell lymphoma; LL, lymphoblastic lymphoma; N/A, not applicable; ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; CLL, chronic lymphocytic leukaemia; CML, chronic myeloid leukaemia; LDH, lactate dehydrogenase; ULN, upper limit of normal; WBC, white blood cell count; TLS, tumour lysis syndrome.

*Other additional risk factors independently place an individual patient into a higher risk category.

Hyperphosphataemia and hypocalcaemia

Malignant cells contain excess intracellular organic and inorganic phosphates compared to non-malignant cells, in some cases up to four times as much (Zusman *et al*, 1973; Flombaum, 2000). The rapid release of these excess phosphates can often quickly overwhelm the ability of the kidneys to excrete phosphate; a situation frequently made worse by the presence of concomitant uric acid nephropathy. Significant hyperphosphataemia usually develops in the first 24–48 h after commencing chemotherapy (Flombaum, 2000; Davidson *et al*, 2004). In patients taking pharmacological doses of corticosteroids, the sudden increase in circulating phosphate may also be partly due to the reduction of tubular excretion of phosphorus that is associated with steroid therapy (Zusman *et al*, 1973).

Hypocalcaemia occurs as a direct result of hyperphosphataemia. Rising phosphate levels caused by the continuing release of excess phosphates from malignant cells coupled with the failure of renal phosphate excretion causes calcium-phosphate to precipitate out in the soft tissues, including in the renal tubular system where it presents as nephrocalcinosis or nephrolithiasis. The intra-renal calcification in turn produces a further deterioration in renal function with consequent worsening of plasma calcium levels (Jones *et al*, 1995). Precipitation of calcium phosphate crystals is at greatest risk of happening *in vivo* when the plasma calcium-phosphate product is ≥4·6 mmol/l (Locatelli & Rossi, 2005).

Hyperphosphataemia has a crucial role in the development of TLS, particularly in patients who later go on to require dialysis (Jones *et al*, 1995). Symptoms of hyperphosphataemia are mainly manifested indirectly through its effect on calcium (Tiu *et al*, 2007). Hypocalcaemia causes lengthening of the QT interval on the electrocardiogram (ECG) and thus may induce ventricular arrhythmias. Other symptoms of clinical hypocalcaemia include muscle cramps, tetany and seizures (Locatelli & Rossi, 2005).

Hyperkalaemia

Hyperkalaemia is often the earliest and potentially the most serious clinical consequence of TLS (Locatelli & Rossi, 2005) and may present as early as 6 h after the start of treatment (Flombaum, 2000). The rapid release of large amounts of intracellular potassium can be acutely life-threatening by inducing cardiac arrhythmias and may even cause sudden death. The rise in plasma potassium levels will be accentuated in the presence of any significant degree of renal insufficiency. It is also important to avoid iatrogenic hyperkalaemia by ensuring that the intravenous fluids administered during the induction of chemotherapy do not contain added potassium.

Renal failure

Although the development of urate crystals and calcium-phosphate precipitation in the renal tubules are the commonest causes of renal failure during the initiation of cancer therapy, other factors can also be important. Direct renal involvement or physical obstruction of renal outflow by malignancies, the use of nephrotoxic drugs and septicaemia can all contribute to the development of acute renal failure, as can some viral infections including H1N1 swine flu (Perez-Padilla *et al*, 2009, Senanayake, 2009).

The consequences of renal failure can be catastrophic. In addition to the immediate worsening of the metabolic disturbances listed above, oliguric fluid retention pre-disposes to pulmonary oedema and hypoxia (Fig 1). Renal dysfunction also causes metabolic acidosis with reduction in plasma bicarbonate levels, which accentuate the effects of hyperkalaemia and encourage further urate deposition in the renal tubules. If left untreated, there is a high risk of multi-organ failure (Locatelli & Rossi, 2005).

The primary aims of the prophylaxis and direct management of TLS are to increase the urinary excretion of uric acid, potassium and phosphate and to avoid the development of renal failure. If this is successfully achieved, the considerable morbidity and early mortality associated with TLS can be prevented.

Clinical management of tumour lysis syndrome

The clinical management of TLS has been greatly aided by advances in the knowledge of the aetiology of the syndrome, improvements in risk stratification of patients at presentation and the development of more effective uricosuric drugs. For the vast majority of patients it is now possible to predict with a high degree of accuracy those who would be likely to develop clinically significant TLS, thus enabling intervention to be started early enough to prevent TLS occurring in the first place. Early intervention is essential to achieve better outcomes (Jeha, 2001).

The critical first step in successful management of TLS in patients presenting with malignancy is to correctly allocate each patient to an appropriate prophylactic regimen prior to the initiation of anti-cancer therapy. Table I sets out a risk categorization strategy for haematological malignancies based on initial assessment at presentation.

In their new TLS risk classification, Cairo *et al* (2010) set out three sequential phases to define individual risk. The first step is to assess each patient for TLS and CTLS as set out in Table II (Cairo *et al*, 2010). Next, the type of underlying malignancy is defined as being of low, high or intermediate risk (Table I) and thirdly a separate assessment is made of the presence of renal dysfunction or renal involvement by the malignancy.

Table II. Definition of LTLS and CTLS. Reproduced from: Cairo and Bishop (2004) With permission from John Wiley & Sons © 2004.

Cairo-Bishop definition of laboratory TLS (LTLS)	
Uric acid	≥476 μmol/l or 25% increase from baseline
Potassium	≥6·0 mmol/l or 25% increase from baseline
Phosphorous	≥2·1 mmol/l (children) or ≥1·45 mmol/l (adults) or 25% increase from baseline
Calcium	≤1·75 mmol/l or 25% decrease from baseline

Modified from Hande and Garrow (1993)

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

Cairo-Bishop definition of clinical TLS (CTLS)
Creatinine* ≥1·5 × ULN† (age >12 years or age adjusted)
Cardiac arrhythmias/sudden death*
Seizure*

Modified from Hande and Garrow (1993)

Clinical tumour lysis syndrome (CTLS) assumes the laboratory evidence of metabolic changes and significant clinical toxicity that requires clinical intervention. CTLS is defined as the presence of LTLS and any one or more of the above-mentioned criteria.

*Not directly or probably attributable to a therapeutic agent.

†Creatinine levels: patients will be considered to have elevated creatinine of their serum creatinine is1·5 times greater than the institutional upper level of normal (ULN) below age/gender defined ULN. If not specified by an institution, age/sex ULN may be defined as: >1 < 12 years, both male and female, 61·6 μmol/l; ≥12 < 16 years, both male and female, 88 μmol/l; ≥16 years, female 105·6 μmol/l; male ≥16 years, male, 111·4 μmol/l.

A few tumour types, notably Burkitt lymphoma and B-ALL carry such an intrinsically high risk of TLS that patients can be allocated to the 'high risk' category even in the absence of additional risk factors. Certain subtypes of acute myeloid leukaemia (AML), myelomonocytic M4 and monoblastic M5 also have been shown to have an intrinsically higher risk of TLS than other types of AML (Montesinos *et al*, 2008). However, for others, an assessment of tumour bulk either in terms of presenting white cell counts in acute leukaemia or physical size or greater than twice normal lactic dehydrogenase (LDH) in lymphomas, is required for risk stratification. The presence of other risk factors, such as oliguria, pre-existing renal failure, pre-treatment hyperuricaemia and even the phase of the malignancy as in chronic myeloid leukaemia (CML), have also to be taken into consideration before allocating patients to appropriate risk groups.

Therapeutic options

Once categorized as 'high', 'intermediate' or 'low risk', each individual patient can be allocated to receive appropriate management; in most cases this will mean a choice of regimens for TLS prophylaxis. However for those with CTLS that is already established at the time of presentation, additional treatment will be necessary to deal with the clinical complications of TLS.

Patient monitoring

The initial clinical management is based on the maintenance of renal output, which is essential for the effective removal of the massive excess of uric acid, phosphate and potassium released into the plasma as a consequence of tumour cell disintegration. All patients require increased fluid intake and close monitoring of fluid output. However for the majority of patients increasing fluid intake alone is not adequate to prevent uric acid crystallization and calcium phosphate deposition in the renal tubules. If this occurs, the loss of renal function due to blockage of the renal tubules further reduces the ability of the kidneys to clear the released toxins, which in turn causes greater increases in the plasma levels of urate, potassium and phosphate and worsening of hypocalcaemia, thus producing the very conditions required for more uric acid and calcium phosphate crystal formation with still further reductions in the renal clearance of toxic metabolites. As the loss of homeostatic regulation spirals out of control, patients are likely to become acutely unwell as a consequence of CTLS (Fig 1).

Monitoring of plasma uric acid, creatinine, potassium, phosphate and calcium is as essential as the strict assessment of fluid input and output. Clearly, the assessment of fluid balance needs to be continuous and in all moderate and high risk patients this should be formally assessed every 6 h. Biochemical testing needs to be at least 12-hourly and, in the higher risk patients, may be required more frequently up to 6-hourly. Hospitals unable to offer round the clock monitoring should consider transfer to another facility.

Monitoring should continue for up to a week depending on the risk category and the presence or absence of CTLS and may need to be continued for a longer period in patients with protracted or unresponsive TLS.

Care has to be taken with the estimation of potassium levels in patients with high white cell counts, particularly where vacuum tube systems are used to send samples from clinical areas to laboratories. Shaking or vibrating high white cell count samples can cause physical disruption of the leucocytes with release of intracellular potassium into the sample plasma thus giving a falsely high estimate of the patient's own potassium level. This can be avoided by having the sample taken promptly and delivered carefully by hand to the laboratory. Capillary samples may also be helpful to prevent the reporting of high, *in-vitro* potassium levels. Uric acid estimation is also prone to pre-analytical errors. A falsely low uric acid level may be found in samples from patients prescribed recombinant uric oxidase (Rasburicase) because the drug remains active *in-vitro* in sample tubes. These must be cooled immediately to deactivate the urate oxidase before laboratory assays are undertaken to ensure that the laboratory results accurately reflect *in-vivo* plasma uric acid levels.

Hydration fluids

All patients should receive an increased fluid intake of usually 3·0 l/m^2 per 24 h. In the low risk group this can be given orally but fluid balance must be monitored closely. Where low risk patients continue initial therapy as outpatients before the initial induction phase is completed, clear advice should be given about how much fluid needs to be taken and to seek advice urgently if urine output unexpectedly reduces. For all other patients hydration fluids are administered intravenously. These should be as hypotonic or isotonic saline solutions i.e. 0·45 saline in 5% dextrose or 0·9 saline and, importantly, no potassium should be added (Navolanic *et al*, 2003).

Drug treatment

In the UK two drugs are used for the treatment of TLS, the oral xanthine oxidase inhibitor, allopurinol, and the exogenous recombinant uric oxidase, rasburicase, which is administered intravenously (Fig 2). Following the introduction of rasburicase, the intravenous form of allopurinol is no longer available in Europe (Navolanic *et al*, 2003). Allopurinol or rasburicase should be given depending on the risk category of the patient and continued for a period of 5–7 d (Navolanic *et al*, 2003).

Allopurinol

Allopurinol is a xanthine oxidase inhibitor that decreases the production of uric acid by reducing the conversion of hypoxanthine to xanthine and xanthine to uric acid (Fig 2).

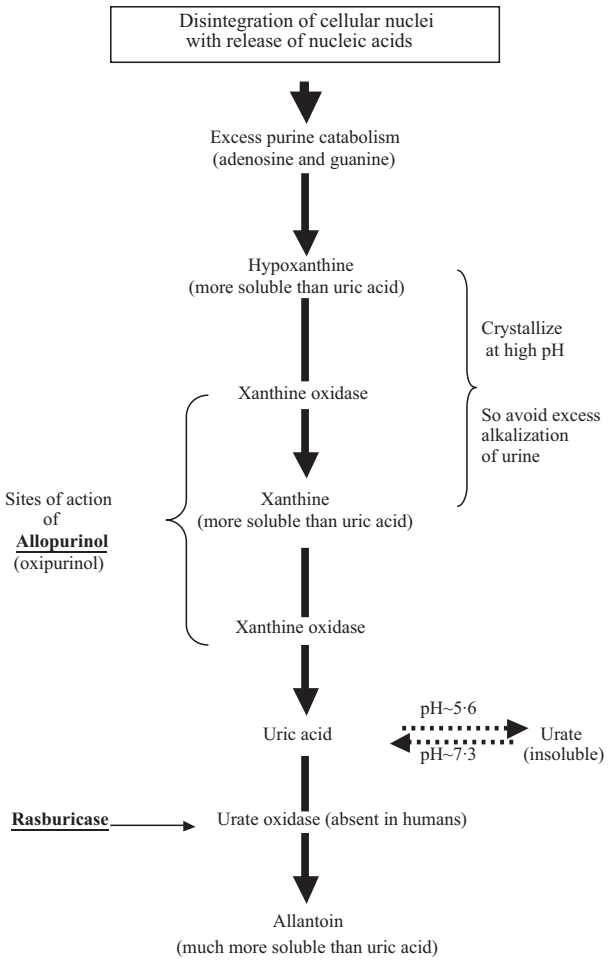

Fig 2. Mechanisms of action of xanthine oxidase inhibitors (allopurinol) and exogenous urate oxidases (rasburicase).

Importantly it does not increase the rate of breakdown of any uric acid that has already been formed. Because both hypoxanthine and xanthine are relatively more soluble than uric acid, this reduces the formation of uric acid crystals in the renal tubules; particularly in the distal tubules where the more acid environment encourages uric acid to precipitate as insoluble urate salts (Hande *et al*, 1981; Pui *et al*, 2001). Allopurinol has a half-life of 60–180 min and its active metabolite, oxypurinol, remains active longer with a half-life of 18–30 h. Oxypurinol is excreted via the kidneys and its half-life is significantly prolonged in the presence of renal failure.

The use of allopurinol in haematological malignancies was first described by Krakoff and Meyer (1965). In the 45 years since their original paper, allopurinol has proved to be effective as prophylactic therapy for patients in the low and intermediate risk categories. It is inexpensive and is administered orally at a dose of 300–450 mg/m^2 per d in three divided doses to a maximum of 400 mg/d in children. Infants <10 kg should be dosed by body weight at 3·3 mg/kg every 8 h (Cairo, 2002). In adult patients a dose of 100 mg/m^2 per dose every 8 h or 200–400 mg/m^2 per d in 1–3 divided doses up to a maximum of 800 mg/d has been recommended (Coiffier *et al*, 2008). Because allopurinol and its metabolites are excreted by the kidney, drug accumulation can occur in renal failure and the initial dose of allopurinol should consequently be reduced. With a creatinine clearance of 0·33–0·17 ml/s, a daily dosage of 200 mg of allopurinol is suitable. When the creatinine clearance is <0·17 ml/s, the daily dosage should not exceed 100 mg. With extreme renal impairment (creatinine clearance <0·05 ml/s), as well as reducing the total dosage, the interval between doses may also need to be lengthened, though in practice most patients with significant renal failure should receive rasburicase instead.

Allopurinol is far from an ideal uricosuric agent. In high risk patients or where there is pre-treatment evidence of TLS, particularly in those patients with high uric acid levels at presentation, allopurinol's slow onset of action of 24–72 h and failure to clear already formed uric acid is a major disadvantage (de Bont & Pieters, 2004; Rampello *et al*, 2006). Side effects occur in 3% of patients receiving allopurinol (Navolanic *et al*, 2003). These include skin rashes and hypersensitivity that may include hepatic dysfunction (Cheson & Dutcher, 2005). If allergic reactions do occur, allopurinol should be stopped immediately to avoid the development of Stevens-Johnson syndrome and the patient should be switched to rasburicase (Andreoli *et al*, 1986; Navolanic *et al*, 2003). Allopurinol also inhibits the degradation of other purines, including purine analogue chemotherapeutic agents, such as 6-mercaptopurine and azathiaprine (Cairo, 2002), whose doses should be reduced by 50–70% (Conger, 1990) or be avoided completely (Cheson & Dutcher, 2005) while allopurinol is being administered.

In the past it was considered standard practice to use urinary alkalinization in conjunction with allopurinol, although there was little if any experimental evidence to support this (Conger & Falk, 1977). The aim was to reduce the rate of insoluble urate crystal formation by keeping the pH in the renal tubular system high. However, this had the deleterious effect of making both hypoxanthine and xanthine less soluble, promoting the deposition of hypoxanthine and xanthine crystals in the renal tubules instead and causing hypoxanthine and xanthine nephropathy.

Rasburicase

Humans and primates lack urate oxidase, the enzyme that metabolizes urate to allantoin (Fig 2), a substance that is approximately five to ten times more soluble than uric acid (Brogard *et al*, 1972; Pui, 2002). This is due to a nonsense mutation that occurred in a common ancestor during the process of evolution (Yeldandi *et al*, 1991). Theoretically, this may have produced an evolutionary advantage because uric acid has antioxidant properties and as such may protect against neurological degenerative processes and by so doing increase longevity (Scott & Hooper, 2001).

Initial studies with non-recombinant uric oxidase derived from the fungus aspergillus flavus confirmed the efficacy of

uric oxidase in the prevention and treatment of TLS. However this form of uric oxidase was relatively toxic with approximately 5% of patients experiencing serious side effects that were mainly allergic reactions, including rashes and bronchospasm (Pui *et al*, 1997, 2001).

The development of a recombinant form of uric oxidase (rasburicase) retained the efficacy of the aspergillus-derived form but with a marked reduction in side effects and improved tolerability (Pui *et al*, 2001; Bosly *et al*, 2003); <2% of patients experience side effects with rasburicase, which are mainly minor allergic reactions with headaches, rashes and itching. Rarely the side effects can be more serious and include wheezing, oedema and anaphylactic reactions. A small number of patients may develop haemolytic anaemia and methaemoglobinaemia (Easton *et al*, 2001; Brant, 2002; Pui, 2002; Browning & Kruse, 2005; Cheson & Dutcher, 2005). Haemolytic anaemia is particularly likely to occur in patients with glucose-6-phophate dehydrogenase (G6PD) deficiency because the production of allantoin from uric acid mediated by urate oxidase releases hydrogen peroxide, which is a potent oxidizing agent (Ducros *et al*, 1991; Pui, 2002). Therefore rasburicase should not be administered to patients with G6PD deficiency, they should instead receive allopurinol. It may be advisable to screen patients at high risk of G6PD deficiency before administering rasburicase i.e. males of African, Mediterranean or Middle-Eastern descent (Cheson & Dutcher, 2005). Because uric oxidase works by metabolizing uric acid to allantoin, it should not be given concomitantly with treatments that interfere with the metabolism of uric acid from purines (Fig 2). So rasburicase should not be given at the same time as allopurinol and urinary alkalinization is contraindicated. There are patients in the low risk and intermediate groups who fail to respond to hydration and allopurinol, and need to be up-graded to the high-risk group and receive rasburicase instead. Rasburicase can be started immediately; no wash out period is necessary (Jeha *et al*, 2005).

Rasburicase is extremely effective in reducing the plasma levels of uric acid and does so within 4 h of its administration, permitting chemotherapy to be started much earlier than would be safe with allopurinol (Pui *et al*, 2001). In a large multicentre compassionate use trial with 996 evaluable patients, all the patients who received rasburicase prophylaxis maintained low plasma uric acid levels despite ongoing chemotherapy. Furthermore, 100% of adults with hyperuricaemia and 98·5% of the hyperuricaemic children responded to rasburicase treatment and dialysis was only required in 30 of the 996 patients, an incidence of 2·8% (Jeha *et al*, 2005). The European equivalent trial, involving 166 children and 112 adults, reported 2 years earlier (Bosly *et al*, 2003). This trial demonstrated a 100% response to rasburicase in both children and adults with only one reported serious event. Results from a randomized trial comparing rasburicase and allopurinol in 52 paediatric patients with leukaemia or lymphoma at high risk of TLS, reported that in the rasburicase arm there was a 2·6-fold reduction in exposure to uric acid compared to allopurinol and at 4 h there was a reduction of 86% of the initial plasma uric acid level in those receiving rasburicase compared to only a 12% reduction with allopurinol (Goldman *et al*, 2001). So perhaps, not surprisingly, hyperuricaemic nephropathy has become a rare event following the introduction of rasburicase (Moreau, 2005).

Rasburicase is administered intravenously at a dose of 0·2 mg/kg per d as a 30 min infusion of the reconstituted drug in 50 ml of normal saline (de Bont & Pieters, 2004). The duration of treatment is variable and is dependent on how rapidly full control of hyperuricaemia is achieved (Coiffier *et al*, 2008). In the trial reported by Jeha *et al* (2005) that involved 1069 individuals, rasburicase was administered for an average of 3 d.

Rasburicase remains effective when used for re-treatment in the same individual. However the level and incidence of anti-rasburicase antibodies may increase with re-use (Pui, 2002). These antibodies usually develop 1–6 weeks after administration of rasburicase. The majority of these antibodies are not neutralizing but there may be an association with the increase in hypersensitivity reactions seen on repeat exposure of patients to the drug (Pui, 2002; Cammalleri & Malaguanera, 2007).

Although extremely effective, the high cost of rasburicase limits its use to those patients at greatest risk of CTLS, patients unable to take oral medication or with an allergy to allopurinol and perhaps also to patients with pre-existing cardiac disease and elderly patients who cannot tolerate a high fluid intake (Rampello *et al*, 2006). However, when given to high-risk patients, it is cost effective mainly due to the reduced time spent in hospital and a reduction in the number of patients requiring renal dialysis. The prevention of renal failure considerably reduces the total cost of treating patients with haematological malignancies (Annemans *et al*, 2003; Candrilli *et al*, 2008).

Other treatment options

There are two treatment options that are becoming less frequently utilized in the prevention and management of TLS: urinary alkalinization and leucapheresis.

Urinary alkalinization

Urinary alkalinization has not been proven to be of therapeutic benefit in reducing the risk of crystallization of uric acid in the renal tubules (Conger & Falk, 1977). Rather, any reduction in the formation of uric acid crystals is off set at least in part by the increased risk of precipitating hypoxanthine and xanthine instead (Andreoli *et al*, 1986). Furthermore, increasing the pH of the plasma also increases the risk of overt, clinical hypocalcaemia by reducing the proportion of ionized (active) calcium ions and, at the same time, encourages the urinary precipitation of calcium phosphate, which is less soluble at a higher pH (Jones *et al*, 1995; Locatelli & Rossi, 2005).

Moreover, by making clinical hypocalcaemia more likely, the need to administer emergency treatment for clinical hypocalcaemia is also increased i.e. giving calcium intravenously. This in turn is likely to aggravate the risk of precipitation of calcium phosphate crystals in the kidneys. Overall, these mechanisms probably negate any advantage that might be gained by urinary alkalinization and its theoretical ability to reduce urate crystal formation.

Leucapheresis

Leucapheresis can rapidly reduce the peripheral blood white cell count by up to 75%. Until the 1990's this was a common practice for the initial treatment of leukaemia patients presenting with very high white cell counts of $>200 \times 10^9$/l, in an attempt to reduce the effects of hyperviscosity and TLS (Eguiguren *et al*, 1992). However the procedure has not been demonstrated to improve prognosis in the long term and in the UK leucapheresis has become an increasingly infrequent therapeutic option, certainly as far as amelioration of TLS is concerned. Furthermore, the rapid action of rasburicase means that those patients with a high white blood cell count who are at greatest risk of TLS can begin therapy 4 h after rasburicase has been administered, which is probably quicker than it would take to complete a single blood volume leucapheresis cycle.

Summary of treatment options

The initial step is to allocate each individual patient into one of the three categories according to the perceived risk of CTLS (Table I). A typical treatment allocation scheme is outlined in Table III.

Management of complications

The management of the complications of TLS requires a multidisciplinary team approach with the involvement of nephrologists and intensivists. It is important that the advice of other specialists is sought early in the development of a deteriorating clinical situation. Emergency treatment may be required to reverse worsening biochemical parameters or to deal with the symptomatic clinical consequences of the patient's deranged biochemistry. Where this initial therapy is ineffective or the abnormality recurs, the majority of patients will require intensive nursing care and monitoring and will often go on to need renal dialysis.

Table III. Outline of treatment schemes for tumour lysis syndrome.

Risk category	Management
Low	Intravenous/oral fluids, 3 l/m^2 per d and Allopurinol
Intermediate	Intravenous fluids, 3 l/m^2 per d and Allopurinol
High	Intravenous fluids, 3 l/m^2 per d and Rasburicase

Oliguria and fluid retention

The maintenance of hydration and a high fluid output is critical to the prevention and effective management of TLS and its clinical complications. All fluid losses must be taken into account including vomiting and diarrhoea. In some patients oliguria due to physical obstruction of the renal outflow tract by tumour masses will need prompt intervention.

Close monitoring of fluid input and output and regular creatinine estimations are essential. Infants and young children will need to be weighed twice daily to ensure an accurate estimation of their fluid balance. Urine output should be maintained at >4 ml/kg per h for infants and >100 ml/m^2 per h for older patients. Particular care needs to be taken in infants, patients with pre-existing cardiac or renal disease and the elderly.

Any reduction in renal output needs to be taken seriously with an immediate thorough re-evaluation of the clinical situation, ensuring that adequate volumes of fluid have been administered and a prompt re-assessment of the biochemical parameters. It is important to be certain that the patient is not volume-depleted before considering diuretic therapy as diuretics may encourage the precipitation of urate in renal tubules if administered to a patient who is not fluid replete (Jones *et al*, 1995). Emergency treatment for fluid overload is with frusemide at 0·5 mg/kg by intravenous injection. Loop diuretics, such as frusemide, may be less effective in the presence of renal tubular blockage by urate and/or calcium phosphate (Rampello *et al*, 2006). Mannitol may be used as an alternative. If simple measures do not improve urine output or the biochemical parameters have significantly deteriorated, i.e. a creatinine >1·5 times above the laboratory upper limit or a significant age-adjusted increase (Table II), specialist renal advice should be sought with regard to the need for dialysis.

Hyperuricaemia

Hyperuricaemia can be associated with a variety of symptoms including nausea, vomiting, lethargy, anorexia and haematuria as well as oliguria and anuria (Rampello *et al*, 2006). A uric acid level of ≥476 μmol/l or 25% increase from baseline (Table II) suggests the possible development of CTLS. Any patient not already on rasburicase should be switched to this from oral allopurinol. Uric acid levels should ideally be measured at 6-hourly intervals along with the other TLS biochemical parameters. If this fails to correct the hyperuricaemia or rasburicase is contraindicated because of G6PD deficiency, the need for dialysis should be discussed urgently with the renal team.

Hyperphosphataemia and hypocalcaemia

The abrupt release of high levels of phosphate from malignant cells and the associated deposition of calcium phosphate in the soft tissues, including in the renal tubules, is usually control-

lable by hydration and the maintenance of a high urine output. When this fails and the plasma levels of phosphate reach ≥2·1 mmol/l (children) or ≥1·45 mmol/l (adults) or a 25% increase from baseline (Table II), there is a significant risk of CTLS.

High phosphate levels are difficult to control other than by dialysis. Some reduction can be made using oral phosphate binders, such as aluminium hydroxide 50–150 mg/kg per d four times a day for a maximum of 1–2 d (Sallan, 2001; Coiffier *et al*, 2008). But these are slow to act and poorly tolerated by ill patients and children and so are seldom used except perhaps if the patient is considered unfit for dialysis or as a temporary measure in situations where immediate access to renal dialysis is not available.

Asymptomatic hypocalcaemia should not be treated, even with calcium levels of ≤1·75 mmol/l or if there has been a 25% decrease from baseline (Table II), although continuous cardiac monitoring is required. In the presence of cardiac arrhythmias, seizures or tetany, calcium gluconate should be given at a dose of 1 g for adults (10 ml of a 10% solution) by slow intravenous injection over approximately 10 min under continuous ECG monitoring (Coiffier *et al*, 2008) or in children at a dose of 20–30 mg/kg of calcium gluconate; for older children this approximates to 200–500 mg (2–5 ml of 10% solution) and for infants no more than 200 mg (not more than 2 ml of a 10% solution). This will reverse the clinical effects of hypocalcaemia in the short term but will further increase the deposition of calcium phosphate in the renal tubules, exacerbating the overall situation. Uncontrolled hyperphosphataemia and symptomatic hypocalcaemia are indications for dialysis.

Hyperkalaemia

As well as the well-described cardiac effects of hyperkalaemia with typical ECG changes of peaked T waves, prolongation of the PR interval and widening of the QRS complex and risk of life-threatening dysryhthmias, high plasma potassium levels may also be associated with lethargy, myasthenia and paresthesia or paralysis (Rampello *et al*, 2006).

Hyperkalaemia of ≥6·0 mmol/l or a 25% increase from baseline (Table II) should be considered as serious and mandates continuous cardiac monitoring.

Plasma potassium levels of ≥7·0 mmol/l constitute a medical emergency. Plasma potassium levels can be reduced quickly by increasing the intracellular uptake of potassium from plasma. There are several ways to achieve this. A beta agonist, such as salbutamol, can be given either as a nebulized inhalation or intravenous injection over 5 min to rapidly reduce plasma potassium levels (Dosage:- by intravenous injection: Neonate 4 μg/kg as a single dose; repeat if necessary; Child 1 month–18 years and adults >18 years, 4 μg/kg as a single dose; repeat if necessary or by inhalation of nebulized solution: Neonate 2·5–5 mg as a single dose; repeat if necessary; Child 1 month–18 years and adults >18 years 2·5–5 mg as a single dose; repeat if necessary). Alternatively, an intravenous infusion of soluble insulin (0·3–0·6 units/kg per h in neonates and 0·05–0·2 units/kg per h in children over 1 month) with glucose 0·5–1 g/kg per h (5–10 ml/kg of glucose 10%; or 2·5–5 ml/kg of glucose 20% via a central venous catheter) can similarly quickly reverse the effects of a high potassium level. Sodium bicarbonate (1–2 mmol/kg) given by intravenous slow bolus may also be effective (Coiffier *et al*, 2008); caution must be taken to ensure that the bicarbonate does not extravisate and bicarbonate must not be given at the same time as intravenous calcium.

Acute cardiac toxicity should be treated with an immediate, slow infusion of calcium gluconate, 1 g for adults (10 ml of a 10% solution) by slow intravenous injection over approximately 10 min under continuous ECG monitoring (Coiffier *et al*, 2008) and for children 20–30 mg/kg; for older children this approximates to 200–500 mg (2–5 ml of 10% solution) and for infants no more than 200 mg (not more than 2 ml of a 10% solution), again administered over 10 min with continuous ECG monitoring. However, as the effects of these manoeuvres are usually short lived, renal dialysis is usually required to maintain safe plasma levels of potassium.

The oral ion-exchange resin, Kayexalate®, has been used to treat moderate hyperkalaemia (Sallan, 2001) but its slow onset of action, poor tolerability and potential for inducing colonic necrosis in the critically ill (Scott *et al*, 1993) make ion exchange resins unsuitable for most patients. Nevertheless, these resins may be useful in circumstances where dialysis is not possible as may be the case in unstable, elderly patients.

Renal dialysis

The definitive treatment for uncontrolled TLS or CTLS is renal dialysis. Following the introduction of rasburicase, hyperuricaemia has become a less frequent indication for dialysis than oliguria and the other biochemical disturbances associated with TLS.

Peritoneal dialysis (PD), haemodialysis and the various forms of haemofiltration have all been used in the context of TLS and CTLS. Peritoneal dialysis is less effective than the others. Clinical improvement is slower with PD, which takes an average 48 h to control the clinical situation (Deger & Wagoner, 1972). Furthermore, the presence of hepatosplenomegaly and abdominal lymphadenopathy and the increased risk of infection in the presence of neutropenia often preclude its use.

There are no major studies comparing haemodialysis and the different forms of haemofiltration (Rampello *et al*, 2006); all appear to be effective and improve the clinical situation quickly and can be expected to rapidly address fluid overload and reverse biochemical abnormalities (Jones *et al*, 1995). Dialysis may need to be continued for several weeks until there is adequate recovery of urine output and renal function. There is evidence that starting haemodialysis early on in the clinical course of CTLS may improve the outcome in patients with multi-organ failure (Rampello *et al*, 2006).

Summary

The management of TLS has been greatly improved through better understanding and classification of the underlying biochemical mechanisms involved. This has enabled the development of an effective system for the categorization of individual patients into appropriate risk groups that determine the type of treatment to be administered. Close monitoring of patients both for accurate fluid balance and the development of biochemical abnormalities enables clinicians to up-grade patients into higher risk categories early on in the course of TLS and thus ensures the timely introduction of more aggressive therapy. The development of rasburicase for use in high-risk patients has significantly reduced the need for dialysis for hyperuricaemia alone. For those patients that fail prophylactic therapy a multi-disciplinary approach is required, as patients will often need intensive care and renal dialysis.

Future considerations

Although the modern management of TLS described above is undoubtedly effective, there are two obvious areas for improvement. A less expensive urate oxidase that could be given orally would mean that more patients could benefit from the improved speed of action of urate oxidase compared to that of allopurinol. A recent report of the cloning of *Bacillus subtilis* urate oxidase expressed in *Escherichia coli* may potentially be further developed to produce an efficient and more cost-effective source of recombinant urate oxidase (Pfrimer *et al*, 2010). Furthermore, there is clearly an urgent need for drugs to improve the excretion of phosphates and to prevent the deposition of calcium phosphate in the renal tubules.

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