Guidelines for the management of tumour lysis syndrome in adults and children with haematological malignancies on behalf of the British Committee for Standards in Haematology

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The guideline group was selected to be representative of UK-based medical experts. Recommendations are based on review of the literature using MEDLINE and PUBMED up to December 2013 under the heading: 'tumour lysis syndrome'. The writing group produced the draft guideline. Review of the manuscript was performed by the British Committee for Standards in Haematology, BCSH Haemato-oncology Task Force, BCSH Executive Committee and by the haemato-oncology sounding board of the British Society for Haematology (BSH). This comprises over 50 members of the BSH who have reviewed the guidance and commented on its content and applicability in the UK setting. It has also been reviewed by representatives from Leukaemia and Lymphoma Research but they do not necessarily approve or endorse the contents. The 'GRADE' system was used to quote levels and grades of evidence (www.bcshguidelines.com). The objective of this guideline is to provide healthcare professionals with clear guidance on the management of patients with tumour lysis syndrome (TLS). The guidance may not be appropriate to every patient and in all cases individual patient circumstances may dictate an alternative approach.

Recommendations

Prophylaxis of Tumour Lysis Syndrome (TLS)

- Patients due to receive chemotherapy for any haematological malignancy should have a risk assessment for TLS (Grade 1B)
- Low risk patients can be managed with careful attention to the monitoring and measurement of fluid status and laboratory results with a low threshold for recourse to intravenous fluids and consideration of allopurinol if needed (Grade 2C)
- Intermediate risk patients should be offered up to 7 days of allopurinol prophylaxis along with increased hydration post-initiation of treatment or until risk of TLS has resolved. (Grade 2C)
- High risk patients should be offered prophylaxis with rasburicase along with increased hydration (Grade 1B)
- Rasburicase should be avoided in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Such patients should be treated with fluids and allopurinol and monitored carefully. (Grade 2C)
- Urate assays, taken whilst patients are receiving rasburicase, must be sent to the laboratory on ice to prevent falsely low assay results. (Grade 1B)
- In high risk adults, in the absence of established clinical or laboratory TLS, TLS can be prevented in the majority of patients using a single fixed dose of 3 mg rasburicase, but this must be followed by careful monitoring of clinical and biochemical parameters with repeat dosing if required. (Grade 2C)
- In high risk children, in the absence of established clinical or laboratory TLS, prophylaxis can be achieved in the majority of patients using a single dose of 0·2 mg/kg rasburicase. Treatment needs to be followed by close laboratory and clinical monitoring for evidence of progressive TLS (Grade 2C). Whilst it seems reasonable to use, as in adults, a fixed dose of 3 mg rasburicase, it is not possible to make a firm recommendation on the basis of current evidence.
- Where rasburicase is being used in the treatment or prophylaxis of TLS, the addition of allopurinol is unnecessary and has the potential to reduce the effectiveness of rasburicase (Grade 2C)
- Urinary alkalinization is not recommended in TLS prophylaxis (Grade 1C)

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Treatment of Established Tumour Lysis Syndrome

- The management of established TLS requires a multidisciplinary approach with involvement of haematologists, nephrologists and intensive care physicians (Grade 1C)
- If facilities are not available locally for intensive management and monitoring, consideration should be given to the transfer of the patient to an intensive care/high-dependency facility or to a haematology centre offering a higher level of care, as defined by British Committee for Standards in Haematology criteria. (Grade 1C)
- Potassium must not be added to the hydration fluid. (Grade 1A)
- Alkalinization of the urine is not recommended in the treatment of TLS. (Grade 1C)
- Allopurinol, whilst useful in the prophylactic setting, is not the drug of choice in established TLS (Grade 1B) except in the presence of G6PD deficiency or allergy to rasburicase.
- In the absence of contraindications, patients with established TLS should be given rasburicase at a dose of 0·2 mg/kg/day. The duration of treatment should be determined by the clinical response. (Grade 1B)
- Asymptomatic hypocalcaemia should not be treated. (Grade 2C)
- Symptomatic hypocalcaemia should be treated with a short infusion of calcium gluconate at a dose applicable to the age/weight of the patient and close monitoring of calcium levels, phosphate levels and renal function (Grade 1C)
- Patients with potassium levels ≥6 mmol/l or having experienced a 25% increase in potassium level from baseline should have cardiac monitoring. (Grade 2C)
- Intractable fluid overload, hyperkalaemia, hyperuricaemia, hyperphosphataemia or hypocalcaemia are indications for renal dialysis. (Grade 1A)
- Peritoneal dialysis (PD) is not recommended for the treatment of TLS. (Grade 1C)
- Dialysis should continue until there is adequate recovery of renal function, resolution of severe electrolyte imbalance and recovery of urine output.(Grade 1A)
- Balanced or isotonic solutions should be administered to maintain urine output >4 ml/kg/h for infants and 100 ml/m^2/h for older patients (Grade 2C)

Introduction

First described by Bedrna and Polcák (1929) in patients with chronic leukaemia treated with radiotherapy, tumour lysis syndrome (TLS) is a metabolic syndrome caused by the breakdown of malignant cells. It is characterized by hyperuricaemia, hyperphosphataemia, hyperkalaemia and hypocalcaemia. The consequences are potentially severe and include acute kidney injury, cardiac arrhythmias, seizures and even death (Will & Tholouli, 2011). TLS can affect patients of all ages, typically in the first few days after the start of chemotherapy. TLS has also been observed in patients with haematological malignancies given radiotherapy (Yamazaki *et al*, 2004), steroids (Sparano *et al*, 1990; Coutinho *et al*, 1997), immunotherapy (Yang *et al*, 1999) and as spontaneous TLS secondary to the high turnover of the tumour itself (Jasek & Day, 1994).

TLS is caused by the excessive release of nucleic acids, proteins and intracellular metabolites from tumour cells, which overwhelms the normal homeostatic control mechanisms and leads directly to increases in plasma uric acid, phosphate, potassium and a reduction in plasma calcium (Locatelli & Rossi, 2005). TLS is particularly likely to occur during induction chemotherapy when there is high tumour burden and tumour cells have a particularly high rate of cell turnover and an increased sensitivity to antimitotic agents. Other factors may also increase the risk of developing TLS, including an elevated serum lactate dehydrogenase (LDH) level, extensive bone marrow involvement, pre-existing renal disease or reduced urinary output (Ribiero & Pui, 2003; Davidson *et al*, 2004). There is some evidence that elderly patients may be at increased risk (Locatelli & Rossi, 2005). In a minority of patients the metabolic derangements are already present before the start of treatment, most often in patients with B-cell non-Hodgkin lymphoma (B-cell NHL), particularly Burkitt leukaemia and lymphoma and acute lymphoblastic leukaemia (ALL) (Jasek & Day, 1994; Alkhuja & Ulrick, 2002; Hsu *et al*, 2004). In some cases TLS develops unexpectedly in patients presenting with apparently low TLS-risk malignancies.

Definition of tumour lysis syndrome

Definitions of TLS have evolved for both adults and children over the last two decades. Patients may have metabolic abnormalities alone (laboratory TLS) or both laboratory and clinical problems (clinical TLS). In many cases laboratory TLS will herald clinical TLS, though clinical TLS can be prevented in many patients with appropriate therapy. The Cairo-Bishop definition of TLS (Cairo & Bishop, 2004) is shown in Table I. It can be seen from the table that the laboratory syndrome is defined by specific electrolyte abnormalities immediately before, during or just after treatment for malignancy. The clinical syndrome is manifest by the development of organ failure or other symptoms caused by the electrolyte imbalance.

There has been some debate with regard to the importance or otherwise of the criteria for definition based on 25% changes from baseline. It is, in our opinion, fair to say that these individual calculations are not usually performed by clinicians. Nonetheless, the importance of monitoring and responding to the trajectory of any change in electrolyte balance is absolutely fundamental to good management and dictates the frequency of monitoring as well as therapeutic interventions.

Pathophysiology

The metabolic effects of TLS are caused by the release of intracellular potassium, phosphate and nucleic acids, the

Table I. Definition of tumour lysis syndrome according to Cairo and Bishop (2004). Reproduced with permission from Cairo, M.S., & Bishop M. Tumour lysis syndrome: new therapeutic strategies and classification. *British Journal Haematology*, **127**(1):3–11 © 2004 John Wiley and Sons Inc.

Laboratory tumour lysis syndrome
The presence of two or more of the following abnormalities in a patient with cancer or undergoing treatment for cancer within 3 days prior to and up to 7 days after initiation of treatment
Uric acid ≥476 μmol/l or 25% increase from baseline
Potassium ≥6·0 mmol/l or 25% increase from baseline
Phosphate ≥2·1 mmol/l or 25% increase from baseline (Children) ≥1·45 mmol/l or 25% increase from baseline (Adults)
Calcium ≤1·75 mmol/l or 25% decrease from baseline
Clinical tumour lysis syndrome
A patient with laboratory tumour lysis syndrome and at least one of
Creatinine ≥ 1·5 × ULN (age >12 years or age-adjusted)
Cardiac arrhythmia
Sudden death
Seizure

ULN, upper limit of normal.

catabolism of which produces large amounts of excess uric acid. In patients with a high tumour burden, the normal homeostatic mechanisms for dealing with the release of cellular contents from dying cells are often overwhelmed, causing laboratory and then clinical TLS.

The first observed effect of TLS is often hyperkalaemia. This can occur as quickly as 6 h after the start of chemotherapy and may be severe enough to be immediately life threatening (Flombaum, 2000; Locatelli & Rossi, 2005). Simultaneously, as a direct consequence of hyperuricaemia, uric acid crystals precipitate out in the renal tubules, particularly in the acid environment of the distal renal tubules, causing a reduction in the ability of the kidneys to excrete the products of cellular disruption (Will & Tholouli, 2011). Renal function becomes further compromised when the released phosphates increase the plasma phosphate concentration and calcium phosphate begins to crystallize out in the soft tissues, including in the renal tract. The development of acute kidney injury causes further increases in plasma potassium levels and the consequent acidosis accelerates the crystallization of uric acid in the renal tubules (Jones *et al*, 1995); at this point the situation spirals out of control, causing a cascade to clinical TLS.

Risk factors for tumour lysis syndrome

There are a number of well recognized risk factors for the development of laboratory and clinical TLS; in essence these relate to the volume and rapidity of cellular breakdown, which may be spontaneous but is more frequently precipitated by anti-cancer therapy. Risk factors include:

1 High tumour burden
2 High grade tumours with rapid cell turnover
3 Pre-existing renal impairment or renal involvement by tumour
4 Increased age
5 Treatment with highly active, cell-cycle specific agents
6 Concomitant use of drugs that increase uric acid levels including alcohol, ascorbic acid, aspirin, caffeine, cisplatin, diazoxide, thiazide diuretics, adrenaline (epinephrine), ethambutol, levodopa, methyldopa, nicotinic acid, pyrazinamide, phenothiazines and theophylline.

Prophylaxis of tumour lysis syndrome

Whilst clinical TLS is a relatively rare event, affecting around 3-6% of patients with high-grade tumours, the consequences are significant, with one-third of affected patients requiring dialysis and an overall mortality rate in excess of 15% being reported (Annemans *et al*, 2003; Candrilli *et al*, 2008). The key to the management of TLS is recognizing those patients at risk of developing the syndrome and using prophylactic measures to prevent its occurrence. It will be difficult, however, to completely eradicate TLS, as a small proportion of patients with very aggressive tumours develop spontaneous TLS prior to receiving any therapy (Galardy *et al*, 2013).

Uricosuric drugs

In the UK, two drugs are licensed for the prevention and management of clinical TLS: the oral xanthine oxidase inhibitor, allopurinol; and the exogenous recombinant urate oxidase, rasburicase.

Allopurinol is a xanthine oxidase inhibitor. It reduces the production of uric acid by decreasing the rate of the conversion of hypoxanthine to xanthine and xanthine to uric acid (Fig 1). 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). Importantly, it does not increase the rate of breakdown of any uric acid that has already been formed and so its therapeutic effect is delayed by 24–72 h (de Bont & Pieters, 2004; Rampello *et al*, 2006).

Rasburicase is a recombinant form of the enzyme urate oxidase (UO). Urate oxidase is an endogenous enzyme commonly found in most mammalian species, but not humans as a consequence of the acquisition of a nonsense mutation in the coding region during hominoid evolution (Yelandi *et al*, 1991). Rasburicase metabolizes urate to allantoin (Fig 1), a substance that is approximately five to ten times more soluble than uric acid (Brogard *et al*, 1972; Pui, 2002). Rasburicase acts immediately, even on already formed urate. It is extremely effective and will reduce the plasma

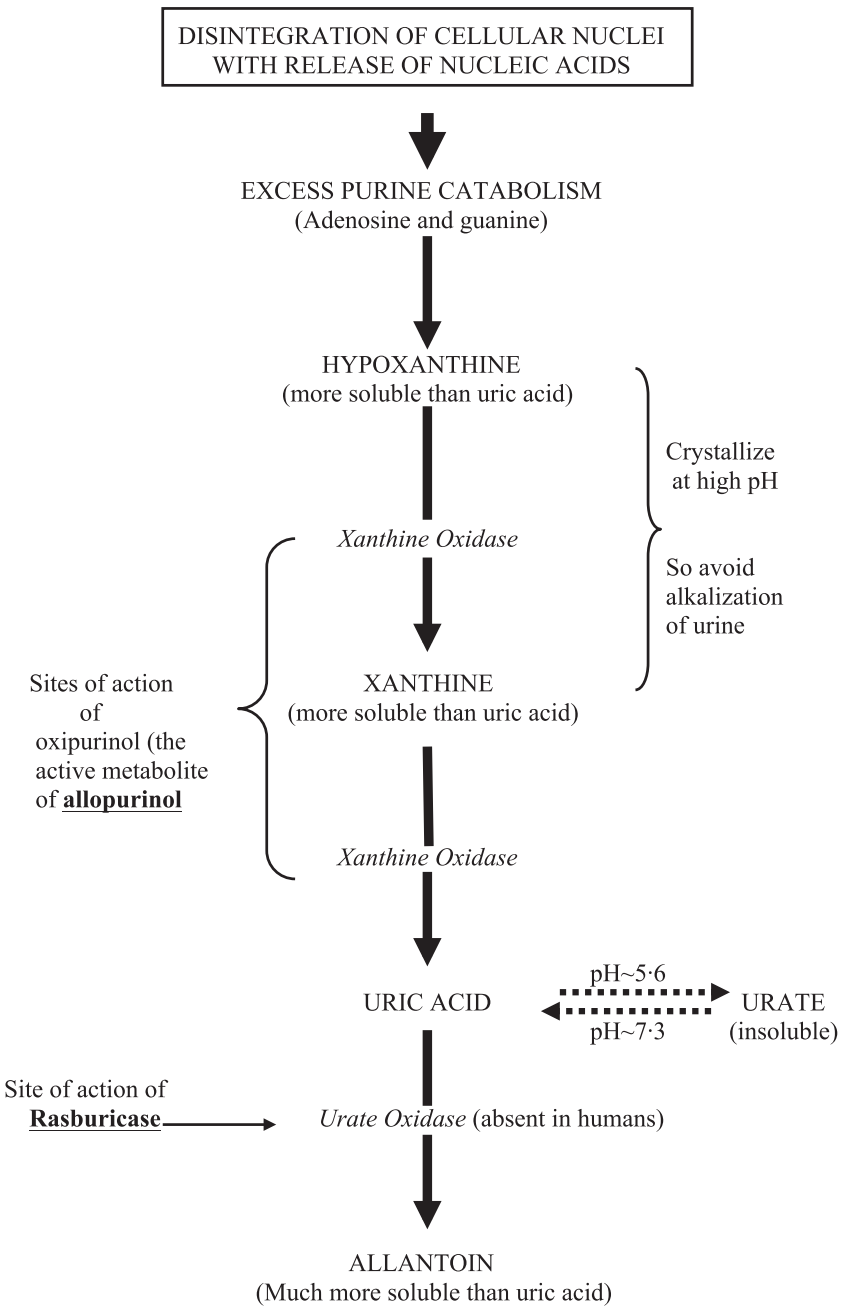

Fig 1. Mechanisms of action of xanthine oxidase inhibitors (allopurinol) and exogenous urate oxidases (rasburicase).

levels of uric acid within 4 h of its intravenous administration, allowing chemotherapy to be started earlier than might be safe with allopurinol (Pui *et al*, 2001).

Given these respective mechanisms of action, where rasburicase is being used in the treatment or prophylaxis of TLS, the addition of allopurinol is unnecessary and has the potential to reduce the effectiveness of rasburicase.

Risk stratification

There are a number of risk stratification models that have been proposed (Cairo *et al*, 2010; Howard *et al*, 2011). Whilst there may be some variation in detailed stratification methodology, the general principles are:

1 To assess whether there is evidence of laboratory or clinical TLS at diagnosis
2 To assess whether the tumour itself confers high risk
3 Assess other risk factors that impact on risk of TLS development, e.g., pre-existing renal failure, advanced age, renal involvement by tumour, efficacy of proposed treatment or use of predisposing concomitant medications.

The international expert consensus panel (Cairo *et al*, 2010) have produced an excellent model to allow stratifica-

tion of patients into 3 main categories: those at low, intermediate or high risk of TLS development. Cairo *et al* (2010) recommended that those at low risk of TLS development be actively monitored and offered hydration +/- allopurinol prophylaxis. Those at intermediate risk of TLS development were recommended to be offered active monitoring, hydration and allopurinol prophylaxis. Those at high risk of TLS development were recommended to be offered active monitoring, hydration and rasburicase prophylaxis.

To our knowledge, there have been no additional publications that fundamentally impact the model proposed by Cairo *et al* (2010). The issue that seems, to our group, most important to address in these current guidelines is which patients are at high enough risk of TLS to warrant administration of rasburicase. We would therefore propose that high-risk patients are identified early as distinct from those requiring hydration +/- allopurinol only.

Those patients categorized as being at the highest risk of developing TLS are planned to have intensive chemotherapy and fulfil the following criteria:

1 Acute lymphoblastic or myeloid leukaemia with WBC $>100 \times 10^9$/l.
2 Burkitt lymphoma or lymphoblastic lymphoma.
3 High-grade lymphoma (diffuse large B-cell lymphoma and T-cell NHL) with bulky disease defined as LDH > twice the upper limit of normal (ULN) or tumour bulk on computerized tomography (CT) scan. The definition of tumour bulk will vary between adults and children. It is generally regarded as a mass >10 cm in diameter in adults.
4 Any patient with haematological diagnosis who has renal impairment or is allergic to allopurinol should be considered for rasburicase despite their risk assignment based on tumour features, though those with low risk disease can often be managed using hydration alone.

Patients fulfilling the criteria for high-risk disease should generally be offered a schedule of monitoring and prophylaxis that includes the use of rasburicase. Patients who do not fulfil these criteria should be offered a schedule of monitoring, hydration and possibly allopurinol. There is little evidence available to inform decisions regarding omission of allopurinol and whether specific patient groups can be determined. What is clear though, is that any form of prophylaxis is only likely to be useful during the first course of treatment and at future time points where re-induction or salvage chemotherapy is used. There is no rationale for using prophylaxis in the setting of consolidation therapy including bone marrow transplant if the patient is in or near to a remission.

Special attention should be paid when patients, even those with low-grade disease, are being treated with potent novel agents. TLS may be seen in the context of lower risk disease in this instance.

Prophylaxis with hydration

The exact fluid volume required is not known but it seems reasonable to aim for 3 l/24 h in adults. In patients at high risk of TLS, the use of allopurinol in association with a forced alkaline diuresis was the traditional method to manage these patients. Uric acid has an increased solubility in an alkaline pH, so giving sodium bicarbonate intravenously might theoretically aid its excretion. However both xanthine and hypoxanthine, that precede uric acid in the biochemical pathway, become less soluble in alkaline conditions and so precipitate before any uric acid can be formed thus negating any potential advantage of the increased solubility of uric acid at high urinary pH. Alkaline diuresis is therefore not recommended (Ten Harkel *et al*, 1998; Coiffier *et al*, 2008).

Prophylaxis with allopurinol

The standard recommended dosing schedule for allopurinol in prevention of TLS is 200–400 mg/m^2/day in 1–3 divided doses for adults, up to a maximum of 800 mg daily. In children, the recommended dose is 300–450 mg/m^2/day in three divided doses up to 400 mg daily. In infants weighing <10 kg the dose is 3·3 mg/kg every 8 h. In practice, most adult haematologists simply use 300 mg/day and, for the most part, this is effective but it may be prudent to increase the dose of allopurinol or, preferably, switch to rasburicase in the presence of deteriorating biochemical or clinical markers., Allopurinol doses may need to be adjusted in renal failure.

Allopurinol should be given for up to 7 days after chemotherapy is started. In patients with an allergy to allopurinol it is generally safe to use prophylactic hydration only along with careful monitoring as patients at very high risk of TLS would be given rasburicase.

Prophylaxis with rasburicase

Rasburicase prophylaxis along with appropriate hydration and monitoring is recommended for patients with the very high-risk characteristics detailed in the criteria above. The drug is licensed for the treatment and prophylaxis of TLS but is contra-indicated in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency.

Rasburicase is highly effective in the treatment of TLS and has been used in prophylaxis but, with the exception of one small underpowered study (Goldman *et al*, 2001), no other formal randomized trial against allopurinol has been performed. The licensed dose is 0·2 mg/kg and the licensed duration of therapy for prophylaxis is 5–7 days. Rasburicase is undoubtedly a highly effective agent in TLS prophylaxis in both adults and children (Coiffier *et al*, 2003; Pieters & Uyttebroeck, 2003; Yim *et al*, 2003; Jeha *et al*, 2005).

Dosing studies. Although the licensed dose of rasburicase is 0·2 mg/kg/day, a number of publications have explored lower doses and shorter courses of therapy. Previous guidelines have reflected these observations; Cairo *et al* (2010) recommended a dose of 0·1–0·2 mg/kg on the first day, repeated daily for up to 7 days. Almost all of these dosing studies have been retrospective analyses of single centre series. There has been one randomized trial comparing a single dose of rasburicase versus five daily doses in patients at risk of TLS (Vadhan-Raj *et al*, 2012). In the single dose arm, patients received rasburicase (0·15 mg/kg), which could be repeated on a daily basis if required at the discretion of the treating physician. 82 patients were included in the trial, of which 40 were in the single dose arm and only six of those required more than one dose. The authors concluded that a single dose of rasburicase was as effective as prolonged therapy for the majority of patients.

Other groups have investigated fixed dosing irrespective of patient weight. Trifilio *et al* (2006) adopted a fixed dose of 3 mg following a serendipitous observation in a single patient. They subsequently used this dose in a cohort of 43 patients with raised uric acid levels receiving a stem cell transplant or chemotherapy for a haematological malignancy. Only six patients required a second dose and there were no significant renal complications in any patient. More recently, this group have published their experience in a larger cohort of 247 adult patients (Trifilio *et al*, 2011). Overall 51/247 patients were treated with a second dose of rasburicase. Treatment failure was defined as failure to normalize uric acid levels 24 h after dosing. In patients with a baseline uric acid level of $\leq$ 0·713 mmol/l, the failure rate was 18% as compared to 84% in those with baseline uric acid level > 0·713 mmol/l.

The efficacy of this lower fixed dose regimen has recently been confirmed in a study of patients at high risk of TLS (Coutsouvelis *et al*, 2012). A 3-mg fixed dose was employed in 42 patients suffering from a range of haematological malignancies, including 13 patients with ALL and ten patients with Burkitts lymphoma. All but 8 of the patients required a single dose, including leukaemic patients with a white cell count over 100×10^9/l. There were no hypersensitivity reactions, no requirement for haemodialysis and no deaths seen in this cohort.

A recent meta-analysis (Feng *et al*, 2013) has looked at the effectiveness of a single fixed dose of rasburicase across 10 studies in adult patients at high risk of developing TLS. Comparison was made with results from patients treated with rasburicase given at the licensed dose for 5 days or patients treated with allopurinol. The single fixed dose ranged from 0·05 mg/kg to 0·20 mg/kg. The pooled response data for the single dose of rasburicase showed that a single fixed dose was as effective as the prolonged rasburicase treatment with respect to the control of uric acid levels but superior to allopurinol. In addition, a single standard dose of rasburicase, defined ≥6 mg, demonstrated non-inferior clinical benefit compared with the licensed dose.

In paediatric practice the first prospective trial evaluating the use of rasburicase for the prevention of TLS has recently been published (Galardy *et al*, 2013). Eighty-five patients, aged 1–23 years, with aggressive B-cell malignancies were treated with rasburicase at the licensed dose (0.2mg/kg) with a single treatment, which was repeated if needed either prior to or subsequent to chemotherapy commencement. The mean number of doses delivered was 1·5 (range 1–6) with 40 patients being given a single dose. In this high-risk cohort, only 5% of patients developed renal impairment after rasburicase administration and none of those patients had hyperuricaemia. Six patients in total required haemodialysis however in five of these it was initiated prior to chemotherapy and the other patient required dialysis for hyperphosphataemia. It is critical to monitor electrolytes following the use of rasburicase.

Taking these data into account, and pragmatically considering available vial sizes, we recommend that, in the absence of established clinical or laboratory TLS, TLS can be prevented in the majority of adult patients using a single fixed dose of 3 mg rasburicase. It is essential to closely monitor for biochemical and clinical markers of TLS and if there is evidence of any progression then the dose should be repeated daily until markers of TLS have entirely returned to normal. Progression to established TLS will require management as described below.

Whilst there is evidence to support the use of a 3-mg fixed dose for prophylaxis in an adult setting, this is lacking in paediatric practise. It would seem very reasonable to extend this approach into children based on the fact that for a fixed dose they will effectively receive a higher dose per kg than adults for whom this practice is effective. In the absence of evidence, however, we cannot make this a firm recommendation. We would, however, advocate further research in this area. As for adult patients, if a single rasburicase dose is used, it is essential to monitor closely for biochemical and clinical markers of TLS. If there is evidence of any progression then the dose should be repeated daily until markers of TLS have entirely returned to normal. If clinical TLS develops despite prophylaxis then patients should be managed with a standard 0·2 mg/kg/day dose of rasburicase as outlined below.

It must be remembered that the presence of rasburicase in the blood will artificially lower urate levels *in vitro* unless samples are sent to the laboratory on ice. Care must be taken that falsely low urate levels are not used to guide therapy.

Recommendations

- Patients due to receive chemotherapy for any haematological malignancy should have a risk assessment for TLS (Grade 1B)
- Low risk patients can be managed with careful attention to the monitoring and measurement of fluid status and

laboratory results with a low threshold for recourse to intravenous fluids and consideration of allopurinol if needed (Grade 2C)
- Intermediate risk patients should be offered up to 7 days of allopurinol prophylaxis along with increased hydration post-initiation of treatment or until risk of TLS has resolved. (Grade 2C)
- High risk patients should be offered prophylaxis with rasburicase along with increased hydration (Grade 1B)
- Rasburicase should be avoided in patients with G6PD deficiency. Such patients should be treated with fluids and allopurinol and monitored carefully. (Grade 2C)
- Urate assays, taken whilst patients are receiving rasburicase, must be sent to the laboratory on ice to prevent falsely low assay results. (Grade 1B)
- In high-risk adults, in the absence of established clinical or laboratory TLS, TLS can be prevented in the majority of patients using a single fixed dose of 3 mg rasburicase but this must be followed by careful monitoring of clinical and biochemical parameters with repeat dosing if required. (Grade 2C)
- In high-risk children, in the absence of established clinical or laboratory TLS, prophylaxis can be achieved in many patients using a single fixed dose of rasburicase 0·2 mg/kg. Treatment needs to be followed by close laboratory and clinical monitoring for evidence of progressive TLS (Grade 2C). Whilst it seems reasonable to use, as in adults, a fixed dose of 3 mg rasburicase, it is not possible to make a firm recommendation on the basis of current evidence.
- Where rasburicase is being used in the treatment or prophylaxis of TLS, the addition of allopurinol is unnecessary and has the potential to reduce the effectiveness of rasburicase (Grade 2C)
- Urinary alkalinization is not recommended in TLS prophylaxis (Grade 1C)

Treatment of established tumour lysis syndrome

Principles

Management of this condition requires a multidisciplinary approach including haematologists, nephrologists and intensive care physicians. The clinical condition of the patient can change very quickly and frequent monitoring is essential. If facilities are not available locally for such intensive management then consideration should be given to transfer the patient to an intensive care/high-dependency facility or to a haematology centre offering a higher level of care as defined by BCSH criteria (Matthey *et al*, 2010). It is essential to have a high index of suspicion for TLS.

Fluid balance

The first step in managing TLS is to maintain a high urine output with vigorous hydration and careful monitoring of fluid balance. The aim is to prevent uric acid crystallization and calcium phosphate deposition in the renal tubules. The build-up of these products in the renal tubules creates a vicious circle of deteriorating renal function leading to worsening hyperuricaemia, hyperkalaemia, hyperphosphataemia and hypocalcaemia. These biochemical abnormalities in turn drive further tubular deposition of uric acid and calcium phosphate.

There are no trials that demonstrate a particular rate of fluid delivery to be better than another but recent reports suggest 3 l/m^2 every 24 h would be reasonable in adults (Tosi *et al*, 2008; Cairo *et al*, 2010; Will & Tholouli, 2011), with the aim of maintaining a urine output of >4 ml/kg/h for infants and 100 ml/m^2/h for older patients. Balanced or isotonic solutions are advised and it is critical that no potassium is added to the hydration fluid. Urine output should be measured at least hourly and a formal assessment of fluid balance should be undertaken at least 6 hourly. Care should be taken to document all fluid losses, such as vomiting or diarrhoea. Infants, the elderly and those with pre-existing cardiac and renal disease are at particular risk of fluid overload. Daily weights can be useful in assessing fluid balance and infants may need to be weighed twice daily to better assess fluid balance.

A reduction in urine output should prompt reassessment of fluid balance and laboratory parameters. Depending upon the underlying disease, it may be appropriate to consider whether there is a physical obstruction to urine flow by tumour, which may require urgent intervention. Clearly, a reduction in urine output may herald worsening renal failure and fluid overload may develop. Care should be taken in using diuretics in this situation. Whilst furosemide 0·5 mg/kg intravenously (IV) can be a useful emergency treatment, the drug may promote tubular uric acid deposition (Jones *et al*, 1995) and is likely to be less efficacious in the presence of renal tubular blockade. The presence of significant fluid overload requires nephrology advice.

Alkalinization of the urine is not recommended due to only equivocal evidence of efficacy and increased risk of calcium phosphate precipitation along with reduced xanthine solubility at increased pH (Coiffier *et al*, 2008; Ten Harkel *et al*, 1998; Van den Berg & Reintsema, 2004; Tosi *et al*, 2008.)

Management of hyperuricaemia. Allopurinol is a xanthine oxidase inhibitor that acts by preventing the development of uric acid crystals in the renal tubules but it does not influence the breakdown of uric acid that has already been deposited. For this reason, allopurinol, whilst useful in the prophylactic setting, is not the drug of choice in established TLS.

In contrast to allopurinol, rasburicase, a recombinant urate oxidase, metabolizes urate directly to the more soluble compound allantoin. Rasburicase can, therefore, break down deposits of uric acid and reduce urate levels significantly more quickly than allopurinol (Goldman *et al*, 2001; Pui *et al*, 2001; Bosly *et al*, 2003; Jeha *et al*, 2005; Moreau, 2005). Any patient who has been on allopurinol as a prophylactic measure should be switched to rasburicase if they develop clinical TLS, the exceptions being patients who have had previous allergic reactions to rasburicase and those in whom it is contraindicated due to G6PD deficiency. In those patients allopurinol should be continued but renal dialysis is more likely to be required.

The standard recommended dose of rasburicase is 0·2 mg/kg/day given as a 30-min infusion. The duration of treatment should be determined by the clinical response. The current European Medicines Agency and US Food and Drug Administration (www.accessdata.fda.gov/drugsatfda_docs/label/2009/103946s5083lbl.pdf) recommendations include daily dosing for up to 5 days. Whilst there are some data to support short duration of rasburicase or reduced dose therapy in the context of prophylaxis there are no data, beyond those of the licensing authority, to guide dosing in the setting of established TLS. It seems reasonable to recommend rasburicase 0·2 mg/kg/day be given for 3–7 days with careful monitoring of electrolytes.

Management of hyperphosphataemia and hypocalcaemia. If hydration and timely administration of rasburicase do not prevent significant hyperphosphataemia, it can be hard to control phosphate levels other than by dialysis. The temporary use of aluminium hydroxide 50–150 mg/kg/day has been described (Sallan, 2001; Coiffier *et al*, 2008) but is slow to act and poorly tolerated, thus is not routinely recommended in this setting.

Asymptomatic hypocalcaemia should not be treated as treatment can precipitate further calcium phosphate deposition in the kidneys. If corrected calcium levels drop below ≤1·75 mmol/l or there has been a 25% drop from baseline (Cairo & Bishop, 2004) then cardiac monitoring is recommended. Symptomatic hypocalcaemia (e.g. cardiac arrhythmia, seizure or tetany) should be treated with calcium gluconate in the standard doses for adults and children. The aim is to treat the symptoms but not to normalize the biochemical parameters.

Hyperkalaemia. The effects of hyperkalaemia, including life-threatening dysrhythmias, are well described. It is recommended that patients with potassium levels ≥6 mmol/l or having experienced a 25% increase in potassium level from baseline should be offered cardiac monitoring. A potassium level ≥7 mmol/l constitutes a medical emergency and dialysis is likely to be required urgently. Standard measures can be taken to reduce potassium levels but the effects are temporary and dialysis is often required. Acute cardiotoxicity should be treated with a short infusion of calcium gluconate with continuous cardiac monitoring. Nebulized or intravenous salbutamol can be effective, as can intravenous infusion of insulin and glucose. Both strategies increase movement of potassium from the extracellular to the intracellular space.

Renal dialysis. The use of urate oxidase therapy appears to have reduced the need for dialysis in patients at risk of TLS. The Berlin–Frankfürt–Münster group studied paediatric patients with Burkitt lymphoma/leukaemia and monitored care and outcomes over an 11-year period (Wössman *et al*, 2003). During the first time period of the study no patients received urate oxidase. In the second period, some were given the drug and in the third it was recommended that all 'high-risk' patients were treated with a urate oxidase. Over the course of the study the incidence of TLS was 20·5% vs. 9·4% in periods one and three, respectively. The corresponding rates of anuria were 15·4 vs 3·8%. Perhaps unsurprisingly, a recent study reported a higher incidence of TLS when a cohort of 153 adults at high risk of TLS was studied. 30·7% of patients developed TLS and TLS was an independent risk factor for acute kidney injury and increased 90-day mortality, even in the rasburicase era (Darmon *et al*, 2013).

Nonetheless, when the measures described have failed to prevent renal deterioration and significant fluid overload, hyperkalaemia, hyperuricaemia, hyperphosphataemia or hypocalcaemia have developed, renal dialysis is indicated.

Peritoneal dialysis (PD) is not recommended for this indication because clinical improvement is slower than with other forms of dialysis (Deger & Wagoner, 1972). In addition, patients may have significant tumour-related abdominal pathology, which would contra-indicate this approach.

There are no major trials comparing haemodialysis with haemofiltration or other extracorporeal therapies and all approaches appear to be effective. Given the continuous release of metabolites into the blood in the setting of TLS, some groups have suggested that daily dialysis may be the best strategy (Tosi *et al*, 2008). In patients who are haemodynamically compromised, continuous renal replacement therapy can be helpful. Dialysis should continue until there is adequate recovery of renal function and urine output.

Recommendations

- The management of established TLS requires a multidisciplinary approach with involvement of haematologists, nephrologists and intensive care physicians (Grade 1C)
- If facilities are not available locally for intensive management and monitoring, consideration should be given to the transfer of the patient to an intensive care/high-dependency facility or to a haematology centre offering a higher level of care as defined by BCSH criteria. (Grade 1C)

- Balanced or isotonic solutions should be administered to keep urine output >4 ml/kg/h for infants and 100 ml/m^2/h for older patients (Grade 2C)
- Potassium must not be added to the hydration fluid. (Grade 1A)
- Alkalinization of the urine is not recommended in the treatment of TLS. (Grade 1C)
- Allopurinol, whilst useful in the prophylactic setting, is not the drug of choice in established TLS (Grade 1B) except in the presence of G6PD deficiency or allergy to rasburicase.
- In the absence of contraindications, patients with established TLS should be given rasburicase at a dose of 0·2 mg/kg/day as a 30-min infusion. The duration of treatment should be determined by the clinical response. (Grade 1B)
- Asymptomatic hypocalcaemia should not be treated. (Grade 2C)
- Symptomatic hypocalcaemia should be treated with a short infusion of calcium gluconate at a dose applicable to the age/weight of the patient and close monitoring of calcium levels, phosphate levels and renal function (Grade 1C)
- Patients with potassium levels ≥6 mmol/l or having experienced a 25% increase in potassium level from baseline should have cardiac monitoring. (Grade 2C)
- Intractable fluid overload, hyperkalaemia, hyperuricaemia, hyperphosphataemia or hypocalcaemia are indications for renal dialysis. (Grade 1A)
- Peritoneal dialysis (PD) is not recommended for the treatment of TLS. Grade 1C)
- Dialysis should continue until there is adequate recovery of renal function, resolution of severe electrolyte imbalance and recovery of urine output.(Grade 1A)

Disclaimer

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Declarations of interest

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Review process

Members of the writing group will inform the writing group Chair if any new pertinent evidence becomes available that would alter the strength of the recommendations made in this document or render it obsolete. The document will be archived and removed from the BCSH current guidelines website if it becomes obsolete. If new recommendations are made an addendum will be published on the BCSH guidelines website (www.bcshguidelines.com). If minor changes are required due to changes in level of evidence or significant additional evidence becomes available to support current recommendations a new version of the guidance will be issued on the BCSH website.

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