Management of the Prevention and Treatment of Tumour Lysis Syndrome in Adults

Background

Tumour Lysis Syndrome (TLS) is a metabolic complication that can occur during chemotherapy or radiotherapy for certain haematological malignancies and very occasionally solid tumours. TLS is characterised by the rapid development of the following:

- Hyperuricaemia
- Hyperkalaemia
- Hyperphosphataemia
- Hypocalcaemia
- Rising LDH, urea and creatinine progressing to acute renal failure (ARF)

The acute release of intracellular products (e.g. urate, phosphate, potassium) into the circulation is a result of lysis of radiosensitive or chemosensitive rapidly proliferating cells. Hypocalcaemia occurs as result of precipitation of calcium phosphate in soft tissues due to the acute development of hyperphosphataemia.
Acute renal insufficiency results from the precipitation of uric acid (common pre-chemotherapy) and/or calcium phosphate crystals in renal tubules (common following chemotherapy).

Risk Factors

There are a number of well recognised risk factors for the development of laboratory and clinical TLS, these 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

Definition

Evidence of **laboratory tumour lysis** syndrome is defined as two or more of the following (after Cario & Bishop):

uric acid*	≥ 476 micromol/l or 25% increase from baseline
oliguria*	despite adequate hydration
potassium*	≥6mmol/l or 25% increase from baseline
Calcium	≤ 1.75mmol/l or 25% decrease from baseline
phosphate*	≥1.45 mmol/l or 25% increase from baseline

For **clinical tumour lysis**, patient must have laboratory features, together with one of creatinine >= 1.5 x upper limit of normal, arrhythmia, seizure or sudden death.

There are two drugs are licensed for the prevention and management of TLS:
Allopurinol and Rasburicase

Risk Stratification for TLS
Risk stratification enables the identification of patients that should be offered active monitoring, hydration and rasburicase prophylaxis, as opposed to the low and intermediate risk groups, in which hydration +/- allopurinol prophylaxis should suffice (perhaps with inpatient monitoring in borderline situations).

High-risk patients can be identified by the following criteria:
- Burkitt's or Burkitt's-like Lymphoma
- Lymphoblastic Lymphoma
- ALL WCC > 100 x 10^9/l
- AML WCC > 100 x 10^9/l
- CML in blast crisis WCC > 100 x 10^9/l
- High-grade Lymphoma with bulky disease – defined by LDH> twice upper limit of normal or tumour bulk >10 cm in diameter

Note:
- Diseases which are traditionally low-risk (e.g. CLL) can become very high risk with the usage of novel therapeutics. Therefore special care must be taken in these therapy-specific circumstances, irrespective of pathology.
- Increasing age, pre-existing renal impairment and renal involvement by tumour are also factors that increase risk and may push the treating clinician to consider specific patients as high-risk

Prevention of Tumour Lysis Syndrome

Low/Intermediate Risk Patients
Low/ intermediate risk patients can be managed with a combination of hydration and allopurinol.
- Aim for total hydration fluid of 2-3 litres/24 hours, start hydration before chemotherapy. Potassium must not be added to the hydration fluid.
- The optimal dose of allopurinol has not been established, but the standard dosing schedule is 200-400 mg/m^2/day in 1-3 divided doses (up to a maximum of 800 mg daily) for up to 7 days. For the most part 300 mg/day 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. Start 24-48 hours prior to chemotherapy if possible. The dose should be reduced when creatinine clearance is < 20ml/min.
- Minimum of daily weight, routine observations and fluid balance
- A select group of intermediate-risk group patients may warrant inpatient monitoring with enhanced hydration and electrolyte monitoring.
- Patients allergic to allopurinol should be considered for rasburicase.

High-Risk Patients
Rasburicase prophylaxis alongside hydration is recommended for high-risk patients as detailed above. **The drug is contraindicated in those with G6PD deficiency;** such patients should be treated with fluids and allopurinol **(**it may be prudent to use

increased doses of allopurinol) and monitored carefully.

Ideally rasburicase should be commenced 4 hours prior to initiation of chemotherapy. The licensed dose is 0.2mg/kg/day IV for up to 7 days, however a meta-analysis reviewing the effectiveness of a single fixed dose of rasburicase in high risk patients concluded non-inferior clinical benefit to the licensed dose for high-risk prophylaxis.

Taking this into account, a **single, fixed dose of 7.5 mg rasburicase for high-risk patients is recommended prior to chemotherapy**, with regular monitoring and application of a second dose if required.

Protocol for the Management of Established Tumour Lysis Syndrome

1. **Liaise with ITU/ renal unit as early as possible**

2. **Hydration**

- Ensure IV fluids are running at greater than 3 litres/ m^2/ day (i.e. twice usual maintenance). It is critical that potassium is **NOT** added to the hydration fluid.
- Aim for urine output greater than 100ml/ m^2/ hr. Monitor urine output hourly.
- Maintain strict fluid balance chart and place urinary catheter
- Assess fluid balance formally every 4 hrs
- Weigh twice daily
- Fluid retention may be treated with IV furosemide (0.5- 1mg/kg) or mannitol (0.5mg/kg) if weight gain is > 3 kg. In the event of severe oliguria or anuria, a single dose of furosemide (2-4mg/kg) may be considered to improve or initiate urinary output

3. **Rasburicase**

- **Initiate rasburicase at 0.2 mg/kg IV for 3-7 days** depending on clinical and biochemical parameters: No dose adjustment is necessary in renal or hepatic impairment.
- **Side effects:** commonly fever, vomiting and nausea. Less commonly diarrhoea, headache, allergic reactions and haemolytic anaemia (in those with G6PD deficiency)
- Refer to Appendix 1 for reconstitution and administration details

4. **Patient Monitoring**

- Obtain biochemistry samples 4 hourly for the first 24 hours after chemotherapy these should include:
  Potassium, phosphate, calcium, magnesium, urea, creatinine and urate
- ‘ Blood sample management and Rasburicase’: The literature is inconclusive with regard the need to manage samples on ice, therefore in order to determine locally any differentiation, the following protocol should be observed until sufficient data is collated, and a local policy can be determined(review December 2016). For OUH samples only:
  1. Samples within hours for the Churchill laboratory: take 2 lithium heparin samples, place in separate bags. Place one sample on ice.

Transport both samples immediately (but not held together) by hand to the Churchill lab and notify the lab that the.

2. Samples out of hours: send one sample as normal to the JR lab, no ice required.

- If there is no evidence of TLS reduce frequency of sampling.
- Vital signs (T, BP, RR, HR, O2 sats) 4-6 hourly minimum, including CVP as clinically indicated
- Hourly urine output measurements
- ECG as baseline and continuous monitoring as indicated(see Hyperkalemia and

5. Treatment of hyperkalemia

- Clinical manifestations include: nausea, anorexia, vomiting, diarrhoea, neuromuscular and cardiac abnormalities.
- Treat according to local guideline for management of hyperkalemia
- The current OUH guideline for the Management of Hyperkalaemia in Adults can be accessed here (link)
- Information re ECG monitoring etc. is contained within the OUH link immediately above, print out the document for pathway management.

6. Treatment of hyperphosphataemia

- Clinical manifestations include: nausea, vomiting, diarrhoea, lethargy and seizures
- 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 but is slow to act and poorly tolerated, thus is not routinely recommended in this setting.
- Avoid calcium supplements except in neuromuscular irritability.

7. Treatment of hypocalcaemia

- Clinical manifestations include: muscular (cramps and spasms, paraesthesias, tetany), cardiovascular (ventricular arrhythmias, heart block, hypotension, prolonged QT interval) and neurological complications (confusion, delirium, hallucinations and seizures)
- **Treatment of asymptomatic hypocalcaemia is generally not recommended as the risk of precipitating metastatic calcification is high, especially in the setting of hyperphosphataemia**
- Symptomatic hypocalcaemia should be treated with IV calcium gluconate as per local guideline (see link below). The aim of treatment is to treat the symptoms but not to normalize the biochemical parameters.
- The current OUH guideline for the Management of Acute Hypocalcaemia in Adults can be accessed here (link)

8. Indications for haemodialysis/ intensive care

- Potassium ≥6.5mmol/L at 4 hours despite interventions
- Rising urea, creatinine or phosphate despite above

- Metabolic acidosis
- Fluid overload unresponsive to diuretics

References

1. Cairo, M.S. & Bishop, M. (2004) Tumour lysis syndrome: new therapeutic strategies and classification. British Journal Haematology, 127, 3–11.
2. Cairo, M.S., Coiffier, B., Reiter, A. & Younes, A. (2010) Recommendations for the evaluation of risk and prophylaxis of tumour lysis syndrome (TLS) in adults and children with malignant diseases: an expert TLS panel consensus. British Journal of Haematology, 149, 578–586.
3. Jones GL, Will A, Jackson GH, Webb NJ, Rule S; British Committee for Standards in Haematology. 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.
Br J Haematol. 2015 Jun;169(5):661-71
4. Feng X., Dong, K., Pham, D., Pence, S., Inciardi, J. & Bhutada, N.S. (2013) Efficacy and cost of single-dose rasburicase in prevention and treatment of adult tumour lysis syndrome: a meta-analysis. Journal of Clinical Pharmacy and Therapeutics, 38, 301–308.
5. Oxford University Hospitals NHS Trust. Guidelines for the management of hyperkalemia in adults, Sep 2015.
6. Oxford University Hospitals NHS Trust. Guidelines for the management of acute hypocalcaemia in adults, Oct 2014.

Appendix 1 –Reconstitution and Administration of Rasburicase
Rasburicase should be ideally given 4 hours prior to commencement of chemotherapy or high dose steroids

- Rasburicase vials contain 1.5mg rasburicase/ml (1.5mg and 7.5mg vials) – please round dose to the nearest 1.5mg
- Reconstitute each vial of rasburicase required with the vial of solvent provided (1.5mg – 1ml, 7.5mg – 5ml). Mix by swirling gently. Do not shake
- Dilute in 50ml sodium chloride 0.9% and infuse over 30 minutes
- The diluted drug can be given peripherally

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Review

Name	Revision	Date	Version	Review date
Dr Graham Collins, Haematologist	Review	July 2011	2.1	July 2013
Dr Jaimal Kothari, Haematologist Cheuk-Kie Cheung, Specialist pharmacist Nadjoua Maouche, Specialist pharmacist Rachel Miller, Ward Sister	Full review: change in Rasburicase management and sampling audit.	March 2016	3.0	December 2016

Sandy Hayes, Quality manager				