Oxford Department of Clinical Haematology

Prevention and Management of Tumour Lysis Syndrome (TLS) in Adults

Background

Tumour Lysis Syndrome (TLS) is a metabolic complication that can occur during systemic anti-cancer treatment (SACT), or radiotherapy, for certain haematological malignancies and very occasionally solid tumours. TLS is characterised by the rapid development of two or more of the following:

- Hyperuricaemia
- Hyperkalaemia
- Hyperphosphataemia
- Hypocalcaemia
- Clinical TLS (laboratory TLS with one or more of the following clinical manifestations: acute kidney injury (rising creatinine), cardiac arrhythmia, seizure or sudden death.

The acute release of intracellular products (e.g., urate, phosphate, potassium) into the circulation is a consequence of lysis of radiosensitive or SACT sensitive 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-SACT) and/or calcium phosphate crystals in renal tubules (common following SACT).

Risk Factors

There are several well recognised risk factors for the development of laboratory and clinical TLS, including:

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, for example: 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 (Cairo & Bishop, 2004):

uric acid	≥ 476 micromol/L or 25% increase from baseline
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

Additional Investigations

- LDH: elevated
- Serum creatinine >1.5 times the upper limit
- Serum urea: elevated
- Urine pH <5
- ECG - arrhythmia

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 (consider 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
- Or WCC < 100 and LDH >2 times upper limit of normal
- High-grade Lymphoma with bulky disease – defined by LDH more than twice the upper limit of normal or tumour bulk >10 cm in diameter.

Note:

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

Prevention of Tumour Lysis Syndrome

1. Low/intermediate risk patients (prophylaxis)

Low/intermediate risk patients can be managed with a combination of hydration and allopurinol.

Hydration	• **Start hydration before anti-cancer treatment.** • Aim for total hydration fluid of 2-3L in 24 hours. • **AVOID** additional potassium in hydration fluids
Medication	• Allopurinol 300mg ONCE daily for 7 days[a], start 24 - 48 hours prior to SACT. • Reduce allopurinol to 100 - 200mg ONCE daily where creatinine clearance (CrCl) is <20ml/min.

[a] This dosing follows standard and established practice within haematology; however, the adult dosing schedule allows 200–400 mg/m2/day in 1–3 divided doses, up to a maximum of 800 mg daily.

Observations:

- Daily weight, vital signs, fluid balance, blood sampling (creatinine, urea & electrolytes; including calcium, phosphate, potassium and magnesium, uric acid, LDH) in addition to usual SACT monitoring.

Additional considerations:

- Minimise use of concurrent nephrotoxic drugs, avoid thiazide or potassium-sparing diuretics.
- 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.

Deterioration during prophylactic treatment

In the case of deteriorating biochemical, or clinical markers, there should be prompt initiation of rasburicase.

In individuals contra-indicated for rasburicase, allopurinol doses can be increased up to a maximum of 800mg/day (in 2-3 divided doses).

2. High-Risk Patients (prophylaxis)

High risk patients should be managed with a combination of hydration and rasburicase.

Hydration	**Hydration should start 2 days before anti-cancer treatment.** **Administer IV fluids to maintain urine output of 100ml/m2/hour** Consider loop diuretic to force diuresis if not adequate. **AVOID** additional potassium in hydration fluids
Medication	Rasburicase 3mg IV stat 30-60mins prior to anti-cancer treatment. A second dose can be considered within individual cases. For G6PD deficient individuals: Allopurinol 200 – 400mg/m2/day in 1-3 divided doses, up to a maximum of 800mg daily

Rasburicase prophylactic dosing

The licensed dose is 0.2mg/kg/day IV for up to 7 days (Sanofi, 2021), however a meta-analysis reviewing the effectiveness of a single lower fixed dose of rasburicase in high-risk patients concluded non-inferior clinical benefit to the licensed dose for high-risk prophylaxis (Feng et al, 2013).

British Society of Haematology (BSH) recommends a fixed dosage of 3mg in the prophylactic setting (Jones et al, 2015) which has since been adopted by several Trusts across the UK.

We endorse the recommendation for a single, fixed dose of 3mg rasburicase for high-risk patients prior to SACT, with regular monitoring and application of a second dose if required.

Commented [CN(O1]: As above

Observations:

- Daily weight, vital signs, fluid balance, blood sampling (creatinine, urea & electrolytes; including calcium, phosphate, potassium and magnesium, uric acid, LDH) in addition to usual anti-cancer treatment monitoring.
- Note: out of hours a venous blood gas must be taken and tested in parallel to standard laboratory bloods as there is no on site out of hours biochemistry lab at the Churchill. The standard bloods should be couriered the John Radcliffe Hospital urgently.

Additional considerations:

- Minimise the use of concurrent nephrotoxic drugs, avoid thiazide or potassium-sparing diuretics.
- Several contra-indications to rasburicase treatment exist, please refer to Appendix 1.

Deterioration during prophylactic treatment

In the case of deteriorating biochemical, or clinical markers, there should be prompt escalation to the full protocol for management of established TLS.

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/m²/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/ m²/ hr. Monitor urine output hourly.
- Consider loop diuretic to force diuresis if not adequate.
- Biochemistry every 6 hours or the first 24 hours after diagnosis
- Maintain strict fluid balance chart and place urinary catheter.
- Assess fluid balance formally every 4 hours.
- 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.
- **Where rasburicase is contra-indicated** - ensure maximum dose of allopurinol is administered (up to max 800mg daily in 2 - 3 divided doses).
- Refer to Appendix 1 for contra-indication, side-effects, reconstitution, and administration details.

4. Patient Monitoring

- A patient with established TLS can deteriorate rapidly, and close monitoring is essential to anticipate escalations in care.
- Clinical monitoring:
  - Vital sign monitoring (SaO2, RR, HR, BP and temperature) at least 4 to 6-hrly
  - Urine output monitoring on an hourly basis
  - Weight, at least daily
  - Clinical examination of fluid status at least 6-hrly
  - ECG monitoring at baseline, and as indicated (see Hyperkalaemia and Hypocalcemia sections below)
- Blood monitoring
  - Check potassium, phosphate, calcium, magnesium, urea, creatinine and urate at least 6-hrly initially, using blood gas samples in parallel to acquire rapid potassium values.
  - Blood sample management and rasburicase:
    - Following administration of rasburicase, uric acid levels continue to drop in vitro and so urate results will be spuriously low making interpretation difficult. This effect can be mitigated, though not completely avoided, by immediately placing the sample on ice and rushing it to the biochemistry laboratory for rapid assay. This is not always feasible in day-to-day practice; in which case the biochemical and clinical picture should be taken in its entirety to guide management.
- If there is no evidence of TLS reduce frequency of sampling.

5. Treatment of hyperkalaemia

- 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 management of hyperkalaemia can be accessed on the Medicines Information Leaflets (MILs) directory on the intranet, other Trusts should reference their local guidance.
- 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 aluminum 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. The aim of treatment is to treat the symptoms but not to normalize the biochemical parameters.
- The current OUH guideline for management of hypocalcaemia can be accessed on the Medicines Information Leaflets (MILs) directory on the intranet, other Trusts should reference their local guidance

Sodium bicarbonate: Alkalinisation of urine using sodium bicarbonate to raise the urine pH is no longer recommended.

8. Indications for haemodialysis/intensive care

- Potassium ≥ 6.5mmol/L at 4 hours despite interventions
- Rising urea, creatinine or phosphate despite above
- Central nervous system toxicity secondary to uraemia
- Metabolic acidosis
- Fluid overload unresponsive to diuretics

References

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diseases: an expert TLS panel consensus. British Journal of Haematology, 149, 578–586

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.

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

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Review

Author: (V 1.0): Claire Humphries, Specialist Pharmacist

Audit: These processes are subject to the OxBMT/IEC audit programme

Circulation: NSSG Haematology Website

Name	Revision	Date	Version	Review date
Dr Graham Collins, Haematologist	Review	Jul 2011	2.1	Jul 2013
Dr Jaimal Kothari, Haematologist Cheuk-Kie Cheung, Specialist Pharmacist. Nadjoua Maouche, Specialist Pharmacist. Rachel Miller, Ward Sister. Sandy Hayes, Quality manager	Full review: change in Rasburicase management and sampling audit.	Mar 2016	3.0	Dec 2016
Faouzi Djebbari, Advanced Haematology Pharmacist	Change in timing of rasburicase administration	Feb 2020	3.1	Jun 2020
Yisu Gu, Haematology SpR. Edmund Watson, Haematology SpR. Donna Constantine, Advanced Haematology Pharmacist Denise Wareham, BMT Senior Specialist Nurse	BMJ Best Practice updates; **Rasburicase patient monitoring;** out of hours access to rasburicase; G6PD high risk populations; Additional minor amendments	Dec 2021	3.2	Dec 2023
Donna Constantine, Advanced Cancer Pharmacist Lymphoma NSSG Review Meeting	Rasburicase prophylactic dosing recommended as 3mg fixed dose as per BSH guidance	Jul 2023	4.0	Dec 2024

Appendix 1- Rasburicase administration, contra-indications, and side-effects

Presentation

Rasburicase 1.5mg in 1ml vial; Rasburicase 7.5mg in 5ml vial

Dosing

- **Prophylaxis of TLS**: 3mg IV as a single dose 30 – 60mins prior to anti-cancer treatment or high-dose steroids*. [Unlicensed]
- **Treatment of TLS:** 0.2mg/kg IV ONCE daily for 3 – 7 days as necessary
    - Round all doses to the nearest 1.5mg vial

**This dose may be repeated once more in individual circumstances.*

Side effects

- **Very common (≥1/10):** Headache, diarrhoea, vomiting, nausea, fever
- **Common (≥1/100 - <1/10):** Allergic reaction (rash, urticaria)
- **Uncommon (≥1/1,000 to <1/100):** Haemolysis, haemolytic anaemia, methaemoglobinaemia, severe hypersensitivity, hypotension, bronchospasm
- **Rarely**: Anaphylaxis and involuntary muscle contraction has been reported.

Contra-indications

Rasburicase treatment is contraindicated in:

- Allergy to rasburicase, or excipients
- Glucose 6-phosphate dehydrogenase (G6PD) deficiency
- History of haemolytic anaemia, or presence of other cellular disorders known to cause haemolytic anaemia.
- Methaemoglobinaemia

G6PD deficiency is common in individuals originating from Africa, Asia, the Mediterranean region, and the Middle East; it can also occur less frequently in all other individuals. G6PD deficiency is more common in males than it is in females. A G6PD test is recommended before commencing treatment in individuals with strong heritage from or originating from these areas. G6PD test results may not be immediately available upon request and so should be requested pro-actively during patient diagnostic work-up.

Reconstitution and administration

- Medication is stored within the fridge.
- Reconstitute each vial of rasburicase required with the vial of solvent provided. 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.

Supply out of hours (OUH Specific)

- 3 x 7.5mg rasburicase vials are stored within the fridge of the Churchill Hospital emergency drug cupboard (EDC), and 2 x 7.5mg vials within the JR EDC fridge for out of hours use.
- Between 6pm – 9pm the CH EDC access key can be obtained from UGI ward. This key will require signing out and you will have to present a Trust ID badge. Between 9pm – 8am contact the Night Nurse Practitioner via Switchboard for access to the EDC.
- Access at the JR Hospital differs and can be accessed via security after pharmacy closes, normally between the hours of 12am – 8am, when the resident is not on site.
- If the EDC stock is missing, please contact the on-call pharmacist via Switchboard.